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MUCOLYTIC EXPECTORANT THERAPY WITH AN IODINATED GLYCERYL ETHER

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PROPER ATTENTION to bronchial evacuation will significantly help patients with asthma, emphysema and chronic bronchitis. Unfortunately, however, often overlooked is the fact that bronchodilators and antihistaminic agents cause bronchial secretions to become dry and viscid. Similarly, antibiotic therapy, if indeed effective, will curb the enzymatic proteolytic activity otherwise afforded by bacteria. As a result, bronchial secretions may become more tenacious as the bacterial population is reduced.

To make the sputum less viscid and easier to expectorate, potassium iodide is most generally used. Its action is thought to be related to the rapid excretion of iodides via the bronchi with outpouring of thin watery respiratory tract fluid (RTF).[1]

Other traditional expectorants include the ammonium salts, antimony potassium tartrate, terpin hydrate, guaiacol and its glyceryl ether, creosote, squill and ipecac. Attempts to determine their true effectiveness have met with many technical problems. A reliable objective method of evaluation has yet to be found. Nevertheless, measurements of the increase in RTF after various medications indicate that the iodides are by far the most effective.[2] For maximum benefit they are taken in doses approaching maximum tolerance; this high dosage, coupled with chronic use, also results in a rather high incidence of side effects and frank iodism.

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TABLE I. COMPARISON OF IODINATED GLYCERYL ETHER WITH SSKI

	Drug Reactions (Iodism)	Thyroid Enlargement	Preferred Other Drug	Failures Helped by Other Drug	Gastric Upset
100 consecutive cases using the iodinated glyceryl ether (10 drops 3 times a day)	0	0	2	0	0
100 cases using SSKI (10 drops 3 times a day)	4	3	98	20	5

In order to reduce side effects and intolerance to iodides, we have for some time used an iodinated glyceryl ether* instead of potassium iodide. Table I shows a comparison of observations with this compound and with saturated solution of potassium iodide (SSKI).

When results obtained with this agent in the course of one year were compared with our previous results with potassium iodide, we were surprised to find some unexpected differences which could not be explained by the fact that we were dealing with a better tolerated form of iodide. These differences may be summarized as follows:

1. By using the iodinated glyceryl ether we could reduce the total iodine intake to about one-twentieth of that necessary when using potassium iodide.

2. A number of asthmatic patients who showed good improvement with the iodinated glyceryl ether failed to show similar improvement when given potassium iodide solution.

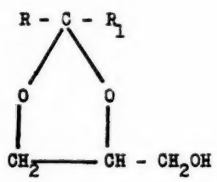
3. Asthmatic children reportedly slept better and were more relaxed when on the iodinated glyceryl ether; no such tranquilizing effect was reported with potassium iodide.

We have searched for an explanation of the unexpected findings enumerated above. The iodinated glyceryl ether appears effective notwithstanding a marked reduction in iodine content as compared with SSKI. The preparation contains 25 mg of iodine per ml, whereas SSKI contains 760 mg of iodine per ml. While potassium iodide is rapidly absorbed and excreted, the iodinated glyceryl ether is slowly absorbed and slowly metabolized.[3] Thus, a small dose of the latter may be effective over a longer time, which may in part explain the lower dosage requirement. One wonders, however, whether the non-iodine moiety of the molecule does not also contribute to its mucolytic action in an as yet unexplained fashion.

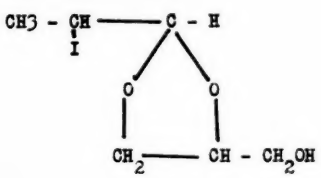
The tranquilizing or relaxing effect observed with this agent was not observed with the use of K-iodide and therefore cannot be ascribed to the iodide moiety of this preparation. A closer look at its actual structure reveals that it contains a 2-substituted-4-hydroxymethyl-1,3-dioxolane con-

*Supplied in the form of 5 per cent solution, Organidin® Solution, by Wampole Laboratories, Stamford, Connecticut.

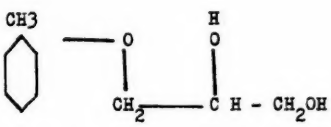
figuration (Fig. 1). Berger and his associates[4] demonstrated that compounds of this configuration have a marked muscle-relaxing action similar to that caused by simple monoethers of glycerol, as for instance, mephenesin or myanesin. Large doses given intraperitoneally can cause complete muscular



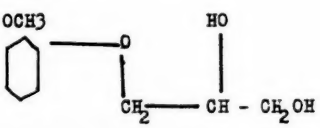
(A) Basic Nucleus Carrying "Relaxing" Effect



(B) 2- Iodo-Propylidene Glycerol (Organidin)



(C) O- Cresol Glyceryl Ether - (Mephenesin)



(D) - Glyceryl Guaicolate

Fig. 1. Formula showing common denominator in "expectorant-relaxors."

paralysis with decrease of muscle tone, while the spontaneous respiration and certain reflexes such as a knee jerk and wink reflex are maintained even during profound paralysis. Small doses, which did not cause any detectable changes in the behavior and appearance of the test animals, protected them from the effect of lethal doses of strychnine and metrazole.[4]

In view of these findings, it is not surprising that the iodinated glyceryl ether gave benefit to our asthma patients over and above the benefits which could be ascribed merely to iodides.

The low iodine content of this mucolytic preparation has certain obvious advantages. In effective dosage, the patient receives a total daily amount of iodine of approximately 80-120 mg. This daily dosage is below the critical level of 200 mg, iodine per day, which would cause significant changes of the total protein bound iodine (PBI) measurement, as recently pointed out by Friend[5] who studied this same agent. A spot check with protein-bound iodine tests in approximately 10 per cent of our own treated patients revealed that the PBI did not exceed the normal limit of 8 micrograms per cent in any.

In addition, the incidence of reactions to iodide is greatly reduced. Fontana[6] and Segal[7] pointed out that about 80 per cent of their iodide-sensitive patients could take the iodinated glyceryl ether without showing signs of intolerance. In our own group of 100 consecutive cases, no instance of iodism or of thyroid enlargement occurred, while among 100 patients using potassium iodide, four showed iodism and three developed thyroid enlargement.

There were no complaints of gastric irritation, although this is fairly often encountered with potassium iodide. This is partly explained again by the low iodine content, but also by the fact that iodine is not liberated from the compound while in contact with the acid contents of the stomach. Thus, Krantz[8] showed that the iodinated glyceryl ether in high concentration did not cause any mucosal irritation, while Lugol's Solution of equal iodine content caused marked irritation and microscopic ulceration.

There are other varied uses for this versatile iodide preparation which might be mentioned in passing. We have found the 5 per cent solution an excellent therapeutic aerosol for asthma, emphysema and asthmatic bronchitis. The glycerol aids in producing a stable aerosol of small particle size, and the iodide is non-irritating and acts to liquefy tenacious sputum. This can be used by itself or added to any of the usual epinephrine or Isuprel aerosols.

The older physician is well aware of iodide as a "cold pill." Before the antihistamines took the stage as "cold tablets," iodides were one of the products frequently used in cold remedies. We have found that the antihistamines frequently produce inspissated mucus, particularly in asthmatic patients, and we have been using the iodinated glyceryl ether in tablet form as an alternative for the antihistaminic cold tablet. It proves effective for relief of the stuffy nose and sore chest of the cold, without the risk of producing tenacious sputum.

SUMMARY

Iodinated glyceryl ether was used over a period of one year or longer in a group of 100 patients. It proved superior to potassium iodide in mucolytic-

expectorant potency. It had a wider margin of safety; could often be used when potassium iodide was not tolerated. Because of its glyceryl ether moiety, the compound has certain properties not obtainable with iodide therapy alone. Outstanding in this respect is its muscle-relaxing and tranquilizing action, which was of particular benefit to our pediatric patients.

The importance of bronchial evacuation through liquefaction of mucus is emphasized, and the use of a mucolytic-expectorant agent is recommended whenever bronchial conditions are being treated with antihistaminics, bronchodilators, and antibiotics, as these agents may cause the sputum to become viscid and thereby will impede expectoration.

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AN AUTHOR'S BEST FRIEND

The author who has a chief, associate or friend willing to study his writings critically is fortunate indeed. Such scrutiny is a time-consuming job. It may require many hours to read and constructively criticize a report of moderate length. But the value of this contribution to an author is immeasurable. Because of the closeness with which he has lived with the subject, he may have neglected significant facts; he may not have realized all the implications of the data; and he may have overlooked work of direct bearing on his own. In addition, the critic may suggest improvements in organization of the paper and uncover errors in grammar or composition. Although it may be disappointing to have to rewrite a paper, it is better to do this than to learn about errors after publication. A properly functioning editorial board works with the same idea in mind.—J. E. ECKENHOFF, M.D., Editorial reprinted from *Anesthesiology*, Vol. 19 (July-August) 1958.

CLINICAL USE OF A NEW ANTIHISTAMINE AND ANTISEROTONIN DRUG: CYPROHEPTADINE

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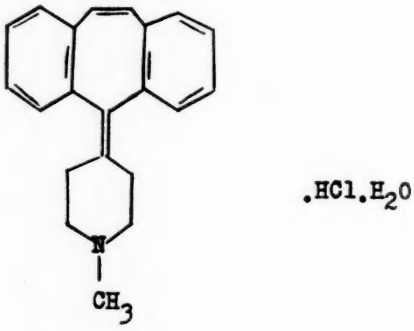
CYPROHEPTADINE is a new antihistaminic drug with the following chemical structure:



It is methyl-4-(4-dibenzo-[*a*, *e*]-cycloheptatrienylidine)-piperadine hydrochloride monohydrate.

In animal experiments, cyproheptadine was found to be a potent antagonist to various effects of histamine. It antagonized the vasodepressor, bronchoconstrictor, and spasmogenic effect of histamine in various species in test situations. It exerted protective action against passive and active anaphylaxis and was capable of blocking histamine-induced gastric secretion, a property not usually found among antihistaminic agents.[1] Cyproheptadine also possessed potent antiserotonin properties, as shown by its ability to antagonize a wide variety of effects due to serotonin, such as its vascular action in dogs, its spasmogenic effect on the isolated rat uterus, its bronchoconstrictor effect in guinea pigs, its ability to increase capillary permeability and its lethal effect in Hemophilus *pertussis-treated* mice. It seemed to be as active as LSD-25 in these studies. Neither cyproheptadine nor LSD-25 blocked serotonin-induced intestinal hyperactivity in the un-

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With the technical assistance of Miss Kay Slemmer, B.S., Miss Marion Beyer and Miss Joan Sansweet. The blood histamine levels were performed through the courtesy of Dr. Leland Brown.

anesthetized dog.[2] Because of the possible role of serotonin in allergic states and the known participation of histamine in such conditions, and because of the potent antihistaminic and antiserotonin effects of cyproheptadine, it was decided to evaluate this agent in various allergic disorders in the Allergy Clinic of Hahnemann Hospital. Because of the dual pharmacologic properties of cyproheptadine, it was hoped that this agent might have a broader spectrum of activity than conventional antihistaminic drugs. Therefore, patients with all types of allergic diseases were included in the study without particular emphasis being placed on any single disorder.

MATERIAL AND METHODS

Sixty-one patients with allergic disorders were selected from the Allergy Clinic of Hahnemann Hospital. Fifty-one patients completed the study; ten failed to return. The age of the former ranged from five to sixty-nine years, and the group consisted of thirty-six females and fifteen males. A clinical summary of the patients is shown in Table I. Except for three cases (Cases 58, 59, 61), the symptoms were found to be allergic in nature by means of the history, skin testing, or both. In most instances the patients were observed by one or more of the investigators for a period ranging from several months to several years prior to the beginning of the study; many had previously received other antihistaminic agents.

The fifty-one patients presented the following disorders which were active during the time of observation: fourteen patients had allergic rhinitis as a primary complaint; fourteen had bronchial asthma, nine of whom also had active rhinitis; nine patients had various types of allergic dermatitis; three had reactions to skin testing; three patients had tension headaches; four had urticaria; two had angioneurotic edema; one had generalized pruritus; and one had an anxiety reaction. There were no febrile patients included, nor were there those with symptoms referable to lower respiratory tract infection. One patient (Case 38) had cellulitis complicating eczema, but her response was evaluated only after elimination of the inflammatory process. Patients were evaluated for the response of allergic complaints only. The patients who had both asthma and rhinitis were evaluated for the predominant allergic symptom. One patient (Case 53) who had allergic rhinitis and angioneurotic edema was evaluated only for the latter. There were four children; one with angioneurotic edema and three ranging from five to twelve years with reaction to skin testing.

The drug was administered in doses of 2.5 to 30 mg daily depending on the tolerance and the therapeutic response, and was available in tablets of 2, 4 and 5 mg strength. When the therapeutic dose was established, the patient was maintained at this level. The optimal dose for each patient is shown in Table I. Although a few patients, especially children, responded best to doses ranging from 2.5 to 10 mg daily, most of them required more. Thirteen patients responded best to 15 mg daily; an additional fifteen, to 20

TABLE I. SUMMARY ON USE OF CYPROHEPTADINE
(61 Patients)

Case No.	Initials	Age	Sex	Diagnosis	Optimal Dose (mg/day)	Duration of Treatment (days)	Clinical Response
1.	J.D.	51	F	Rhinitis, chronic, allergic severe	15	43	Slight
2.	R.C.	32	F	Rhinitis, allergic	15	42	Marked
3.	D.S.	28	F	Rhinitis, seasonal allergic	16	7	None
4.	H.A.	22	M	Rhinitis, seasonal, allergic ragweed	8	42	Moderate
5.	E.N.	36	F	Rhinitis, perennial, allergic	6	125	Moderate
6.	E.S.	26	F	Rhinitis, allergic, seasonal, ragweed			Failed to return
7.	M.Y.	44	F	Rhinitis, allergic, asthmatic, bronchitis, anxiety secondary	10	29	Moderate
8.	F.B.	30	F	Rhinitis, seasonal and perennial	30	14	Moderate
9.	D.M.	57	F	Rhinitis, allergic	20	128	Marked
10.	L.T.	27	M	Rhinitis, vasomotor	20	70	None
11.	R.W.	26	M	Rhinitis, allergic	15	7	Moderate
12.	B.P.	5	F	Rhinitis, allergic	2.5	6	None
13.	D.D.	40	F	Rhinitis, allergic	30	15	None
14.	H.S.	29	F	Rhinitis, allergic			Failed to return
15.	I.A.	25	F	Rhinitis, allergic	30	65	Moderate
16.	M.E.	48	M	Rhinitis, vasomotor	20	49	Moderate
17.	R.K.	44	F	Asthma, bronchial, rhinitis, allergic	16	14	Moderate
18.	W.W.	34	F	Asthma, rhinitis, pharyngetis, probably allergic, facial pruritus	15	28	Moderate
19.	A.R.	62	F	Asthma, bronchial; rhinitis, allergic	15	21	None
20.	L.L.	32	F	Asthma, rhinitis, allergic	15	56	None
21.	M.S.	53	F	Asthma, bronchial	6	6	None
22.	D.C.	30	F	Asthma, bronchial acute	20	28	Marked
23.	J.A.	39	M	Asthma, bronchial	6	1	None
24.	S.F.	57	F	Asthma, bronchial			Failed to return
25.	F.F.		F	Asthma, chronic			Failed to return
26.	L.J.	44	F	Asthma, chronic			Failed to return
27.	M.Y.	46	F	Asthma, bronchial	15	49	Slight
28.	H.H.	48	F	Asthma, bronchial	6	7	None
29.	C.S.		M	Asthma, allergic rhinitis	20	21	Moderate
30.	C.V.	35	F	Asthma, allergic rhinitis			Failed to return

TABLE I (continued)

Case No.	Initials	Age	Sex	Diagnosis	Optimal Dose (mg/day)	Duration of Treatment (days)	Clinical Response
31.	C.E.	42	F	Asthma			Failed to return
32.	G.C.	23	F	Asthma	20	14	None
33.	K.V.	29	M	Asthma, rhinitis	20	7	Moderate
34.	L.H.	64	M	Asthma, eczema	20	49	Moderate
35.	W.L.	8	F	Asthma, rhinitis, allergic	15	65	Moderate
36.	W.M.	77	F	Asthma, rhinitis, allergic			Failed to return
37.	H.W.	64	M	Dermatitis, chronic Ichthyosis, atopic; basilar artery insufficiency; lues, CNS	20	14	Moderate
38.	J.W.	11	F	Eczema, juvenile, asthma, bronchial; cellulitis, popliteal	6	55	Moderate
39.	A.A.	32	M	Dermatitis, atopic			Failed to return
40.	B.R.	15	F	Dermatitis, atopic; pruritus; asthma, bronchial	15	138	Marked
41.	E.	30	F	Neurodermatitis, chronic	20	14	Marked
42.	F.H.	38	F	Generalized neurodermatitis, pruritus			Failed to return
43.	O.A.		F	Dermatitis, allergic	15	7	Marked
44.	H.A.	46	F	Dermatitis, venenata	20	3	Moderate
45.	B.J.	22	F	Dermatitis, allergic	30	21	Moderate
46.	L.S.	38	F	Neurodermatitis	20	21	Moderate
47.	T.	51	M	Dermatitis, allergic	30	18	Marked
48.	M.R.	59	M	Urticaria, chronic	15	4	None
49.	R.C.	60	F	Urticaria, recurrent	15	85	Marked
50.	T.W.	16	M	Generalized papular eruption of unknown etiology probably allergic; pruritus, generalized	16	63	Marked
51.	W.A.	49	F	Urticaria	30	14	Marked
52.	A.M.	48	F	Angioneurotic edema of lower lip (secondary to grapefruit ingestion); rhinitis, vasomotor	6	7	Marked
53.	E.T.	16	M	Angioneurotic edema of upper lip; allergic rhinitis	6	7	Marked
54.	K.K.	5	F	Reaction to skin testing	2.5	2	Moderate
55.	K.K.	12	F	Reaction to skin testing	10	2	Moderate
56.	K.G.	10	M	Reaction to skin testing	10	4	Moderate
57.	T.C.	38	F	Pruritus	20	21	None
58.	M.C.	38	F	Tension headache, psychophysiological reaction aerophagia	15	35	Slight
59.	B.P.	51	F	Tension headache	6	7	Moderate
60.	M.B.	33	F	Headache, facial pruritus	20	14	Moderate
61.	D.S.	61	F	Anxiety reaction	20	76	Slight

mg daily; and six patients required 30 mg daily. A bedtime dose was needed to provide coverage for the night in fifteen patients; this was particularly helpful to patients with pruritus. The patients were maintained on cyproheptadine for 1 to 138 days with the average maintenance period being thirty-two days. A total of 1,640 patient days was analyzed for this report.

TABLE II. SUMMARY ON USE OF PLACEBO
(16 Patients)

Initials	Age	Sex	Diagnosis	Duration of Treatment (Days)	Response
T.W.	16	M	Pruritus, generalized papular eruption	28	3
J.D.	51	F	Allergic rhinitis	14	1
M.W.	64	F	Pruritus	21	1
M.D.	60	F	Rhinitis	14	2
H.L.	64	M	Asthma	14	0
M.S.	39	F	Bronchial asthma	14	2
M.T.	50	F	Neurodermatitis	42	2
C.M.	66	M	Pruritus generalized	14	0
C.M.	43	F	Quincke edema	28	0
E.D.	41	F	Dermatitis	7	0
C.M.	67	M	Bronchiectasis	14	0
J.R.	17	F	Asthma br.	7	0
T.C.	67	M	Angioneurotic edema	14	3
L.M.	68	F	Dermatitis with pigmentation of the face	14	0
D.E.	50	F	Asthma	14	0
S.B.	51	M	Quincke's edema	14	0

The patients were seen weekly in the Allergy Clinic and were evaluated carefully for relief of allergic symptoms and development of untoward side effects. When possible, therapy with accepted antihistaminic agents was alternated with the use of cyproheptadine to compare effectiveness. In a few cases when the effect was doubtful, placebo therapy was instituted for comparison, but this was not generally feasible due to the troublesome symptoms and the therapeutic urgency. Therefore, a random group of sixteen patients with various allergic disorders was selected in order to establish the incidence of placebo response in comparable patients. Of the sixteen patients, six had dermatitis, two allergic rhinitis, five bronchial asthma and two angioneurotic edema. They were maintained on placebos for fourteen to forty-two days and the average treatment period was 17 days (Table II).

Results have been classed as (a) marked (complete and long-lasting relief), (b) moderate (substantial relief with residual mild complaints), (c) slight (partial relief of symptoms), and (d) none (no relief of symptoms). The first two groups comprise clinically satisfactory responses. Inadequate improvement, even if definite, was classed as slight.

Periodic blood counts were made in order to detect possible bone marrow depression. A toxicology laboratory technician was stationed in the clinic for "on the spot" laboratory tests. A group of patients suffering from various allergic disorders was selected for determination of blood histamine levels prior to, and one to three hours following, the administration of

TABLE III. RESPONSE TO CYPROHEPTADINE

Diagnosis	Number Treated	Improvement			
		None	Slight	Moderate	Marked
Rhinitis allergic	14	3	1	8	2
Asthma	14	6	1	6	1
Dermatitis	9	—	—	5	4
Urticaria	4	1	—	—	3
Angioneurotic edema	2	—	—	—	2
Reaction to skin testing	3	—	—	3	—
Pruritus	1	1	—	—	—
Tension headache	3	—	1	2	—
Anxiety reaction	1	—	1	—	—
Total	51	11	4	24	12

5 mg cyproheptadine. The blood histamine level was estimated by a method of Rosenthal and Tabor.[3]

THERAPEUTIC RESULTS

Table III summarizes the effectiveness of cyproheptadine in the various allergic disorders. It is shown that forty (78 per cent) of the fifty-one patients showed improvement. Thirty-six (71 per cent) of the fifty-one patients reported clinically satisfactory results. While the number of patients in each diagnostic category was relatively small for statistical analysis, it is apparent that the vasomotor rhinitis and allergic skin disorders responded well to this medication. Ten of the fourteen patients with vasomotor rhinitis and seventeen of the nineteen patients with skin manifestations of allergic diseases showed substantial to complete relief of their symptoms. It was of interest to observe good responses in allergic dermatitis, pruritus, urticaria and angioneurotic edema. In the latter group of two cases, the drug was used after initial therapy with epinephrine in the accident ward which had not cleared up the edema. The edema cleared within twelve to twenty-four hours after the initiation of cyproheptadine therapy. The relief of pruritus in several patients was most gratifying. The drug was least effective in bronchial asthma since six of the fourteen patients in this category failed to show any response to cyproheptadine. It should be noted that most of these patients had complications or a chronic advanced asthmatic state. A beneficial effect of cyproheptadine with partial relief of tension headache was noted in three patients, one of whom suffered from allergic cephalalgia. In addition, the drug seemed to exert some sedative tranquilizing action as well.

In a similar group of sixteen patients who were on placebo therapy, clinically satisfactory improvement occurred in five, or 29 per cent. The difference between the drug-treated or placebo-treated patients supports the significance of clinical response to cyproheptadine ($p < 0.02$) (Table IV).

The therapeutic dose varied from 2.5 to 30 mg/day. The 6 mg/day dose was not effective in three of the eight patients. Thirty-one patients tolerated the 15 to 20 mg/day dose well. Six patients required 30 mg/day.

TABLE IV. RESPONSE TO PLACEBO

Diagnosis	Number Treated	Improvement			
		None	Slight	Moderate	Marked
Dermatitis	6	3	1	1	1
Allergic rhinitis	2	—	1	1	—
Bronchial asthma	5	4	—	1	—
Angioneurotic edema	3	2	—	—	1
Totals	16	9	2	3	2

Tolerance did not develop in fifty of the fifty-one patients; in a single patient the loss of therapeutic effect was questionable. The therapeutic response at various doses is summarized in Table V.

Side effects are shown in Table VI. The only side effect encountered at the 6 mg/day dose was "inability to think straight" in one patient (Case 5). She thought that the drug caused "too much tranquilization." This reaction, however, may be functional in this particular patient. Three patients reported drowsiness on 15 to 16 mg/day. The drowsiness subsided after one or two weeks, and all the patients continued to take the drug without

TABLE V. THERAPEUTIC RESPONSE ACCORDING TO DOSAGE

Dosage (mg/day)	Number Treated	Improvement				Side Effects (No. of Patients)
		None	Slight	Moderate	Marked	
2.5	2	1		1		
6	8	3		3	2	1
8	1			1		
10	3			3		
15	13	3	3	3	4	4
16	3	1		1	1	
20	15	2	2	8	3	3
30	6			4	2	
Total	51	10	5	24	12	8

recurrence of this side effect. One asthmatic patient (Case 19) became dizzy, but this dizziness did not necessitate cessation of therapy, and the therapy was stopped only because of lack of response after three weeks. The only serious possible reaction was encountered in a forty-four-year-old woman suffering from vasomotor rhinitis, asthmatic bronchitis and sarcoidosis. She had a leukocyte count of 5,500 per cu mm and a normal differential count prior to the administration of cyproheptadine. During the second week of therapy, the white blood count dropped to 4,300 per cu mm and the differ-

TABLE VI. SIDE EFFECTS WITH CYPROHEPTADINE

Side Effects	Dosage (mg/day)	Number of Patients
Sleepiness	20	1
Disturbance of "straight thinking"	6	1
Dizziness	15	1
Drowsiness (first 2 weeks on the drug)	15	3
Dizziness, drowsiness, headache, aches in knees	20	1

ential count revealed 50 per cent polymorphonuclears, 2 per cent eosinophiles, 42 per cent lymphocytes, 1 metamcelocyte, 1 myelocyte, 2 promyelocytes and 1 myeloblast. The drug was immediately stopped. In the third week the white blood count was 3,230 per cu mm calculated by averaging counts done by several different technicians. The differential count revealed 53 per cent polymorphonuclears, 4 per cent eosinophiles, 1 per cent basophils, 40 per cent lymphocytes and 2 per cent monocytes. The initial immature elements disappeared from the peripheral blood. Eight weeks

TABLE VII. BLOOD HISTAMINE LEVEL BEFORE AMD AFTER A SINGLE DOSE OF 5 MG. CYPROHEPTADINE PER OS

Case Number	Pre-Drug	Blood Histamine (γ/liter) (Post-Drug)		
		1 Hour	2 Hours	3 Hours
62	430	382	305	242
63	388	370	332	305
64	1000	770	309	
	220	208	182	
65	440	328	216	
66	172	194	274	
40	320	246		

after cessation of the therapy the white count rose to 4,750 per cu mm with a differential count of 76 per cent polymorphonuclears, 22 per cent lymphocytes and 2 per cent monocytes. This leukopenia may represent depression, but counts in this range are commonly encountered as coincidental findings. There was a slight drop of hemoglobin during therapy (from 12 to 9-10 gm/100 cc blood) which also promptly improved.

The blood histamine level was estimated before, and one to three hours after, the administration of 5 mg cyproheptadine in six patients (Table VII). There was a considerable variation in the initial blood levels; following the administration of the drug, however, the initial values dropped in one hour in five of the six patients. There was a further drop after two hours in four of the five patients. One patient, an asthmatic (Case 66) showed a paradoxical increase of the histamine level. In another patient (Case 64), the levels were determined twice, and the corresponding figures were 220 γ/liter pre-drug and 208 and 182 one and two hours after drug administration, confirming the drug-induced decrease in blood histamine or histamine-like amine level in this asthmatic patient. The response showed such wide variation that the results with such a small number of patients were not statistically significant. Should the same trend persist as the series is enlarged, it would be highly significant. No formal study was undertaken to compare cyproheptadine with a standard antihistaminic agent although four patients (Cases 3, 37, 48, 52) took tripelennamine after cyproheptadine. In one instance of vasomotor rhinitis (Case 3), tripelennamine was more effective than cyproheptadine. In the second patient (Case 37) with

neurodermatitis, cyproheptadine produced partial to substantial relief, as did tripelennamine. The third patient (Case 48) suffering with chronic urticaria had no relief with cyproheptadine nor with tripelennamine, while hydroxyzine was beneficial. The fourth patient (Case 52) afflicted with angioneurotic edema and vasomotor rhinitis had complete and lasting relief with cyproheptadine and only partial relief with tripelennamine. Thus it was not possible to show a preference for either of the two drugs.

DISCUSSION

Cyproheptadine is a potent agent in the specific therapy of a wide range of allergic disorders. It differs from most antihistamines by possessing anti-serotonin activity. In addition, as mentioned above, this drug was able to block histamine-induced gastric secretion, unlike most of the anti-histamines.

In terms of potency, duration of action and degree of absorption from the gastrointestinal tract, cyproheptadine compared favorably with chlor-pheniramine and pyrilamine both of which are among the most active antihistaminics available.[1]

Cyproheptadine did not seem to have depressant activity in man with doses up to 30 mg per day. In animals, especially cats and monkeys, the effect of the drug resembled chlorpromazine to a great extent, but the drug was also similar to that of scopalamine. Cyproheptadine possesses anti-convulsant activity as evidenced by its antagonism against the convulsant action of both nicotine and electric shock in mice. These effects did not interfere with the use of the drug in man in the dose range used, signifying a good therapeutic index.[2]

Several interesting points are raised by the dual effects of cyproheptadine. It is recognized that antihistamines are not uniformly effective in any given allergic disorder, and some of these syndromes are quite resistant to such therapy. Therefore, it is likely that formation or liberation of substances other than histamine plays a role in the allergic phenomena. These substances may potentiate or produce effects similar to histamine. Anti-histamines may not influence these effects.

Serotonin is a substance which is receiving increased attention as a possible amine involved in certain types of hypersensitivity diseases. In many species, serotonin occurs in the same tissues as histamine. Pharmacologically it acts like histamine in many ways. Release of serotonin from rabbit platelets during *in vitro* anaphylactic reactions has been demonstrated.[4] A recent report suggests the etiologic importance of serotonin, released in a physiologically active form, in rabbit anaphylaxis.[5] More recently, cyproheptadine was found to be effective in suppressing and attenuating microscopic lesions of periarteritis and panarteritis produced by reversed bovine serum subanaphylactic sensitization.[6] It is of interest that potent antihistamines like tripelennamine and diphenhydramine were ineffective in modifying the development of passive sensitization vasculitis.[7,8]

Cyproheptadine seemed to be effective in all common allergic disorders except bronchial asthma. The effect of the drug in urticaria and angioneurotic edema was gratifying and suggested a vascular site of action of the drug. The antipruritic effect of cyproheptadine is probably related to its beneficial effect on the disease process rather than to primary sensory action.

Minimal side effects were noted in this study when doses not exceeding 30 mg/day were given. Neutropenia was observed in one patient but disappeared within eight weeks. This could not be definitely attributed to the drug. Long-term effect of the drug was observed in several patients for periods up to four months without untoward effects.

Higher doses than those used in this study may be employed in the future. It seems advisable to do hematologic and liver-function studies on patients receiving this drug until its long-term safety in humans is further established. A double-blind comparison of its effectiveness and side effects with those of accepted agents is recommended.

SUMMARY

Cyproheptadine was evaluated in fifty-one ambulatory patients. Forty-eight of these suffered from various allergic disorders. The average duration of therapy was thirty-two days. A total of 1,640 patient days was observed. Of the fifty-one patients, forty, or 78 per cent improved. Twenty-four of the forty patients had substantial relief of their symptoms, and twelve patients experienced complete and long-lasting relief of allergic symptoms. Thus thirty-six, or 71 per cent of those treated, responded in a clinically satisfactory fashion. The corresponding figure in a group of sixteen patients treated with placebo was five or 29 per cent. The difference is statistically significant ($p < 0.02$).

The best therapeutic dose was 15-20 mg/day. No definite evidence of tolerance to the drug was observed. The side effects were few and were mainly drowsiness, and dizziness which wore off as the therapy progressed. One case of reversible neutropenia was observed. The drug was most effective in allergic skin disorders and vasomotor rhinitis. It relieved pruritus associated with allergic dermatitis, urticaria and neurodermatitis. The drug was not effective in the majority of patients with bronchial asthma or in anxiety associated with allergic conditions. It was effective in three cases of tension headache. Cyproheptadine lowered the blood histamine or histamine-like amine levels in five of six patients. Cyproheptadine is an effective antihistaminic agent and is useful in the therapy of vasomotor rhinitis and allergic pruritus skin disorders. Further comparative evaluation is recommended.

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WE DO NOT KNOW

We do not know the physical basis of intracellular organization, the principles that sort biochemical processes and diverse molecular realms in space without the aid of rigid mechanical frameworks. We do not know . . . what causes orderly substance transport within cells, nor do we know the motive mechanism of cell locomotion. We do not know how cells recognize each other, their foods, their enemies, and how they can react selectively to this environment. We still have no more than shrewd guesses about the mechanism of protoplasmic reproduction that we call growth . . . nor do we know what activates and checks and reawakens the powers for such growth in development, disease and aging (We do not know) the supracellular principles of field character which order the cellular community both in development and in the coordination of our nervous functions, and whose disturbances may yield freaks in the former case, mental disorders in the latter.—Dr. Paul A. Weiss, Rockefeller Institute for Medical Research, from *Patterns of Incidence of Certain Diseases Throughout the World,* the Committee on Government Operations, United States Senate.

BRONCHIAL ASTHMA DUE TO THE ORGANIC PHOSPHATE INSECTICIDES

A Case Report

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THE WIDESPREAD USE of insecticides and the possibility that they can serve as triggering mechanisms in susceptible persons give cause for concern. A case of bronchial asthma in a man following exposure to an organic phosphate insecticide is the subject of this paper.

A forty-one-year-old laborer employed by a chemical packaging company was examined for the first time in December 1958. At that time, he related the following history:

From the time he started working for the company in 1935 up to the time of his accident in 1956, his work consisted mainly of handling sulphur powder. Contact with this powder caused sneezing, stuffed nose and lachrymation. These symptoms abated in the evenings when he returned home and on his days off. During his vacations at home for three weeks in the summer, the nasal and eye symptoms continued for two days and then disappeared. When he returned to work, the symptoms recurred more severely for a day or two, and then continued as before.

During 1956, he began packaging the organic phosphate insecticides. In September 1956, while he was working with Phosdrin, a leak developed in a can used as a "filler." He removed his mask and gloves to stop the leak and thus inhaled a large quantity of the leaking material. Some of it spilled on his hands. Half an hour later, he suddenly felt weak and had a cold sweat. He was then hospitalized.

In the hospital he was slightly cyanotic, dyspneic and incontinent. He stared straight ahead with round, regular and restricted pupils. Many medium moist rales were heard throughout both lung fields. He was treated intensively with atropine and was discharged in two days. The cough persisted and gradually became more severe and productive of a white frothy sputum.

Three weeks after his discharge, he noticed that on slight to moderate exertion, he wheezed and coughed and became dyspneic. Co-incidentally, he noted that sneezing, stuffed nose and tearing of the eyes occurred and ceased at frequent intervals during the day, especially on contact with any of the powders in the plant. The symptoms became severe during July, August and September 1957, because the season for working with these insecticides extends from March until the end of September.

During the winter of 1957-58 he improved somewhat, but the following spring his chest again tightened and his cough and dyspnea became even more severe than the year before. During this period, he noted that all these symptoms were most severe at bedtime and on arising. He would be awakened, at times during the night, with coughing and wheezing.

In April 1957, he had an attack of pneumonia. In May 1958, he had another

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more severe attack of pneumonia for which he was admitted to the hospital. X-ray examination of the chest at that time showed "patchy, irregular, ill-defined pneumonic-like infiltration involving the entire right lung field—most pronounced in the region of the right upper lobe. The right diaphragm is slightly elevated."

Since his initial attack, any contact with chemicals in the plant, no matter how little, has caused coughing and wheezing and severe dyspnea after the coughing spell. He has had frequent attacks of cough syncope, usually at bedtime and arising. He has been awakened every night by a severe coughing and wheezing attack, not always followed by syncope.

During the year before the first examination, he had become aware of an exquisite sensitivity to house dust, which, on slight contact, set off an episode of sneezing, coughing and wheezing. This has continued up to the present time.

Physical examination, at the time of the first visit revealed the following positive findings: there was moderate edema and slight redness of the nasal mucous membrane. The chest was barrel-shaped with minimal movement on respiration. The lungs were hyper-resonant throughout. There was marked inspiratory and expiratory wheezing with prolonged expiration, more pronounced on the right side.

Fluoroscopic examination revealed fairly adequate movement of the diaphragm and marked diminution of movement of the ribs on respiration. There was hyper-illumination of both lung fields. X-ray examination of the chest at that time showed increased broncho-vascular markings bilaterally, more on the right. The right hilum was widened. The lung fields were otherwise clear.

Complete intradermal skin tests gave positive reactions of clinical importance to house dust and horse serum. The remaining tests were negative.

Lung function tests revealed a Maximum Breathing Capacity of 87 liters per minute (estimated normal, 151 liters per minute); Vital Capacity registered 4200 cc (estimated normal, 4400 cc). Timed Vital Capacity tests were as follows:

Timed Vital Capacity	*Trial No. 1*	*Trial No. 2*
(Seconds)	(Per Cent)	(Per Cent)
1	57	52
2	76	78
3	86	88

These tests were repeated two weeks later with essentially the same findings.

On March 21, 1959, the patient complained of a cough which was accompanied by thick yellow sputum that had occurred during the previous five days. His temperature was 103° F. Physical examination and x-ray examination of the chest indicated right middle lobe pneumonia.

On March 30, 1959, cholinesterase activity determinations were made with the following results:

Red Blood Cells	.72△ ph/hr.
Plasma	.77△ ph/hr.

The results were within normal limits and ruled out the possibility of severe poisoning. Mild poisoning was still a possibility but could not be detected because pre-exposure determinations of the blood-enzyme level had not been made.

DISCUSSION

The sequence of events as they occurred is summarized in order to bring out the occupational relationship:

There is a long history of allergic rhinitis, due to a very mild sensitization to house dust. Aggravation of this condition occurred following exposure

to the irritant action of sulphur. After the severe episode with Phosdrin, bronchial asthma and pulmonary ephysema came on very rapidly. The episodes of pneumonia were related to the asthma. Bronchial block on the right side, with thickened mucous plugs, caused the elevated diaphragm and atelectasis noted in the chest x-ray at the hospital. On two occasions, the lung function tests showed normal vital capacity but the timed-vital capacity and the maximum breathing capacity were diminished. These findings are compatible with the diagnosis of bronchial asthma and pulmonary emphysema.

An irritant[1,2] may act as a localizing factor and may precipitate an allergic reaction in the affected organ. This is a clinical observation rather than an explanation of the mechanism of action. More recently, however, antigen-antibody reactions have been implicated. Vigliani and Pernis[3] showed that inhalation of silica particles resulted in the appearance of intra-cellular lipo-proteins which then acted as auto-antigens. Gross[4] proposed that a mechanism of synergism resulted in reciprocal enhancement of immune reactions to dust and infection. This enhancement would explain the progressive massive fibrosis in the British coal worker's lungs, in tuberculo-silicosis and tuberculo-kaolinosis. The Sterner-Eisenbud[5] theory that beryllium dust denatures proteins which then behave as antigens, is another immunologic approach.

Cholinesterase is normally found in the body in adequate quantity. Its purpose is to destroy acetylcholine as soon as it appears in the tissues. The effect of the organic phosphate insecticides is the irreversible inactivation of the cholinesterase in the nervous system, muscle and secretory glands, with the resultant accumulation of acetylcholine. The symptoms of organic phosphate insecticide poisoning, therefore, are the same as those of acetylcholine poisoning. Daily exposure to concentrations of these compounds which are insufficient to produce symptoms following a single exposure may result in the onset of symptoms after several days. Continued daily exposure may be followed by increasingly severe effects. After symptoms subside, increased susceptibility to small doses persists for several weeks until the tissue cholinesterase is completely regenerated. The severity of these symptoms thus depends on the intensity and intervals between exposures, and the effects are prolonged and cumulative.

The major symptomatic effect is on the respiratory tract when it is the main route of exposure. Grob and Harvey,[6] in an excellent discussion of "nerve gases," state that this group of compounds, on inhalation only, produces local cholinergic effects in the upper and lower respiratory tracts before any systemic absorption occurs. In an interesting experimental study, Tiffeneau and Beauvallet[7] showed that the inhalation of nebulized acetylcholine produced the usual local broncho-constrictor effects, but that there was no systemic absorption. Apparently, acetylcholine was destroyed by the cholinesterase which was present in nearby tissues. This could explain normal or slightly depressed cholinesterase activity in the red blood cells

with severe pulmonary effects from inhalation of the insecticides if the exposure is small but frequent.

There is abundant evidence which implicates acetylcholine as the mediator of allergic as well as nervous phenomena. Moll[8] observed that the attack produced by subcutaneous administration of acetylcholine is indistinguishable from a spontaneous attack in asthmatic subjects. Few normal patients experienced any respiratory disturbance after such injection. This suggests that its effect may be local. Is it possible that when the bronchial tree acts as a "shock organ," the cholinesterase activity is already depressed? Tiffenau and Beauvallet[7] demonstrated that the inhalation of 1 per cent of acetylcholine produced no modification of respiration in normal subjects. In individuals with respiratory insufficiency, however, it caused a diminution of vital capacity of 700 to 1000 cc even when the patient was asymptomatic and when other tests revealed no evidence of disability. Subsequently, Curry[9] was able to produce a decrease in vital capacity with acetylcholine aerosol in eleven patients afflicted with hay fever and in twenty-seven patients with asthma. Normal subjects did not respond.

There are several references in the literature to the allergic sequelae following exposure to the organic phosphate insecticides. Wittich,[10] quoting Hildebrand, stated that several cases of bronchial asthma resulted from the spraying of fields with these insecticides. He observed that these compounds "may aggravate or initiate an attack of asthma or rhinitis as a non-specific irritant acting as a trigger mechanism or as a specific chemical allergen." In a personal communication, Hildebrand,[11] referring to the above cases, stated that "in practically all cases, these patients had some evidence of allergy, whether it ranged from eczema, to hives, to hay fever or asthma at some time in their life." Thompson[12] stated, "In addition to actual acetylcholine poisoning, the possibility of aggravating some disease which is known to be in some way related to increased parasympathetic activities, must be considered. Such diseases include bronchial asthma, Parkinsonism, duodenal ulcer and ulcerative colitis." Forman,[15] in discussing one of the two deaths during field spraying from this cause in the State of Washington, felt that the victim was unusually susceptible to the organic phosphate insecticide. "Those who are in favor of such toxic pesticides feel that this man was allergic to the organic phosphate."

Upholt,[13] in an article on the hazards of the use of the organic phosphate insecticides, stated, "one of the serious clinical problems yet to be solved is the importance of pesticides as allergens. Air samplings and surveys may rule out systemic poisonings among residents with only environmental exposure, but the nature of allergic reactions is such that some individuals may react to concentrations too low to measure chemically." In commenting on this observation, Hayes[14] pointed out that "the direct toxic effects of the organic phosphate insecticides include tightness in the chest, increased secretion of the nasal and other membranes and wheezing. The mechanism has nothing to do with allergy. However, because of the clinical

similarity, a few physicians have confused the two conditions." In this personal communication, he described a study in which asthma among a control group of persons who were not exposed to pesticides showed the same seasonal distribution as that among asthmatic persons who were exposed to pesticides during the spraying season.

SUMMARY

It is postulated that the "susceptibility" or "triggering" occurs only in subjects predisposed to allergy. Subnormal cholinesterase levels in the respiratory tract cause a preponderance of acetylcholine to which these individuals are highly sensitive. Subsequently, new environmental sensitizations can appear.

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ALLERGIC ECZEMATOUS CONTACT DERMATITIS CAUSED BY SENSITIZATION TO GLYCERYL MONOSTEARATE

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CONTACT DERMATITIS caused by sensitization to glyceryl monostearate has not previously been reported. The following case report describes this disorder.

CASE REPORT

Following the use of a particular cream deodorant, a middle-aged woman was referred because of the appearance of dermatitis of the axillae. She had previously used two or three other deodorants without any similar trouble, but after one or two applications of the new preparation, the skin of the axillae, including the domes, began to itch, burn and redden. The patient was patch tested with the deodorant cream itself and the individual ingredients of the deodorant, namely: glyceryl, monostearate, spermaceti, sorbitol, aluminum chlorhydroxide complex, butyl para-hydroxybenzoate and perfume. Strong positive reactions occurred after forty-eight hours but only to the deodorant cream and the glyceryl monostearate. Another deodorant cream used one week prior to the appearance of the dermatitis gave a negative patch test.

Control patch tests with glyceryl monostearate placed on two other individuals also gave negative reactions. One control test was done on a person who had apparently normal skin; the other was done on a person with dermatitis of the eyelids due to a powder base.

After elimination of the suspected preparation, the condition of the patient began to subside. Recovery was uneventful and there have been no further symptoms.

DISCUSSION

Glyceryl monostearate is a partial glyceride widely used, often in conjunction with a little soap, as a surfactant and emulsifier in cosmetics, medicinals and food products. Like the natural fats, the material is well digested and assimilated. Glyceryl monostearate is a tan, wax-like solid possessing a faint odor and the following properties: melting point 56-57°, specific gravity 0.97 (25° C), iodine value 3-4, PH (25° C.) 9.309.7 (3 per cent). It is dispersible in hot water and soluble in hot alcohol and hydrocarbons.[1]

It is widely used, especially by cosmetic manufacturers, and has been listed in the following types of products:[2] analgesic ointment, antibiotic ointment, antiseptic lotion, baby cream, baby lotion, baby oil, cleansing cream*, cold cream, deodorant cream*, face cream, face lotion, face packs, foundation cream*, foundation liquid make up*, hair cream, hair dressing, hair oil, hair and skin fragrance, hair rinse, hand cleaners (industrial), hand cleaners (waterless), hand cream*, hormone cream, lubricating

*"Hypo-allergenic" cosmetics.

cream, laboratory hand protectant, lip rouge*, mascara*, (cream), nail white (liquid), protectant skin cream, rouge* (cream), shampoo (cream), shave cream, skin irritant cream, skin magic, soap (cold cream), soapless soap, soap (waterless), sunburn cream, suntan cream, sun tan lotion, spermicide cream, vaginal cream, vanishing cream, vehicle for medication and wave sets.

Since the aluminum salts in deodorants hydrolyze with the formation of free acids, and other astringents as formaldehyde may be converted into formic acid, the degree of acidity may be an important factor in dermatitis of the axilla.[3] In the above case, however, a strong positive patch test was obtained to glyceryl monostearate while the acid-producing astringents produced negative results. The fact that control patch tests in two individuals (one normal and one skin-sensitive to a powder base) were negative to glyceryl monostearate indicates the reaction was true sensitivity and not irritant in nature. This is further corroborated by the wide use in foods and cosmetics including "hypo-allergenic" cosmetics without previous report of trouble.

SUMMARY

A patient with contact dermatitis resulting from the application of a deodorant cream was patch tested with the ingredients of the cream, and the causative agent was found to be glyceryl monostearate, a substance not previously reported as causing contact dermatitis.

ACKNOWLEDGMENT

Grateful acknowledgment is given to the Texas Pharmacal Company of San Antonio, Texas, for supplying the various ingredients of the deodorant cream for patch testing.

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THE FUNDAMENTAL CHARACTER OF RESEARCH

We . . . naturally classify scientific work according to the degree whereby it affects scientific thought and procedures; according to the amount by which it changes the foundation or structure of science itself. We may call this the fundamental character of the research. Some work is of a more fundamental character than other work simply because it affects a broader area, or because within its narrow area of applicability it has a deep and penetrating effect.—I. B. COHEN, *Science, Servant of Man.* Boston: Little, Brown, 1948.

Progress in Allergy

PEDIATRIC ALLERGY

A Critical Review of the Literature

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(Continued from the March issue)

ANTIMICROBIAL AGENTS (CONTINUED)

A new concept in the treatment of penicillin reactions, the use of penicillinase, was first described by Becker.[662] He reported the treatment of forty-six penicillin reactions with penicillinase. Twenty-four of the patients received this treatment alone and the other twenty-two subjects were given concomitant therapy with various antihistamines and hormones. Of the latter group the author attributed the good response in twenty patients to the penicillinase. Although no systemic reactions were observed, pain at the site of the injection was noted in a few of the patients. He concluded that penicillinase should prove to be an extremely valuable adjunct therapy in the treatment of penicillin reactions. Subsequently other authors reported favorably on the use of this enzyme in the treatment of penicillin reactions.[663-665]

Friedlaender[666] pointed out that the antigenicity of penicillinase is such that the possibility of sensitization from repeated administration must be considered in its use. Subsequent experimental evidence in animals[667] and in man,[668] as well as the clinical observations of anaphylactic reactions occurring following the administration of this enzyme, have demonstrated the importance of Friedlaender's warning.[669-672] (Although theoretically penicillinase appears to be a logical agent for the treatment of penicillin reactions, the reviewers have been reluctant to use this drug for several reasons: (1) the aforementioned inherent dangers of hypersensitivity reactions, and (2) the lack of clear-cut evidence of its beneficial effects. The marked variations in the clinical course of penicillin reactions necessitate well-controlled studies to assess the merits of this preparation. To date none have appeared. Furthermore, most of the subjects studied have received other potent anti-allergic agents simultaneously with the penicillinase, thus further complicating interpretation of the results.)

Pabalate (sodium salicylate, sodium p-aminobenzoate and ascorbic acid) was used by Warren[673] for the treatment of penicillin reactions in a small series of patients. The author concluded that the use of pabalate in the treatment of penicillin sensitivity reactions warrants further investigation.

With passive transfer techniques Berryman and Fisherman[674] demonstrated that serum reagens to penicillin G or V did not react with synnematin or penicillamine. Direct intradermal tests in two persons sensitive

to penicillin G showed a positive skin test to penicillin G and V but a negative test to synnematin and penicillamine. The authors concluded that modification of the chemical structure of the penicillin molecule brought about in replacement of cyclic benzyl or thenyl group by a straight-chain 4-amino, 4-carboxy-n-butyl group or degradation of the penicillin molecule to produce penicillamine results in loss of cross-antigenicity.

Evidence has been presented that the ingestion of penicillin-contaminated milk, as well as the administration of polio vaccine containing penicillin, is capable of producing immediate and delayed generalized allergic reactions in persons highly sensitive to this antibiotic.[675,676] Zimmerman[677,678] in two separate articles, suggested the use of penicillinase as a means of proving hypersensitivity reactions to poliomyelitis vaccine containing penicillin and to dairy products containing this antibiotic. Thompson and Pugh[679] also described a method for the detection and estimation of penicillin in poliomyelitis vaccine. The procedure, which consisted of a chromatographic technique, was capable of detecting 0.001 units of added penicillin per ml of the finished vaccine.

TRANQUILIZERS

Because of the widespread use of the tranquilizers in the management of allergic and dermatologic disorders over the past couple of years, and because of the number of reactions from allergic, toxic and other causes that have been reported following their administration, a separate section of this review will be devoted to these drugs. The literature regarding the tranquilizers is as voluminous as the plethora of prescriptions written for these drugs, and only a few of the many reviews written about these agents will be cited here.[680-685] The indications and some of the principles of administration in children have also been presented in three separate articles.[686-688] In an uncontrolled study, Cone[689] found the use of promethazine suppositories effective in the treatment of vomiting in children. (The reviewers believe that it is rarely necessary to use the phenothiazine drugs to control nausea and vomiting in children and that sedation with one of the barbiturates administered rectally is usually sufficient for this purpose.)

LeVan[690] studied the effects of four different types of tranquilizing drugs —reserpine, chlorpromazine, meprobamate, and hydroxyzine—in the treatment of various dermatologic disorders. Based upon the consistency of response from his clinical observations, it was the author's belief that meprobamate and hydroxyzine were preferable to the rauwolfia and chlorpromazine drugs. Wright[691] also studied the usefulness of these drugs in the treatment of patients with dermatological disorders. He concluded that as a specific modality in the therapy of dermatoses it appeared that tranquilizing drugs had little to offer. The only possible exception was hydroxyzine hydrochloride for patients with nummular eczema. As adjunctive therapy, however, he felt that these drugs were helpful in three different situations: when pruritus is severe, when patients have difficulty in sleeping, and when steroid dosage is being reduced.

A number of the so-called tranquilizers have been subjected to double-blind studies. By this technique Koteen[692] studied the effects of meprobamate (Miltown,® Equanil®) on emotional tension and muscle discomfort as compared to that of the matching placebo. In the doses administered, meprobamate had no greater effect in relieving symptoms than did the placebo. The author further pointed out that there is some danger that after prescribing a so-called "tranquilizing agent" the physician may lose interest in the basic problems of his patient.

Of greater interest to the allergist and pediatrician were the double-blind evalautions of trimeprazine as an anti-pruritic by London[693] and by Anderson and Chalmers.[694] The statistical analyses of both of these investigative data revealed that trimeprazine as an anti-pruritic agent was superior to the placebo. Other authors[695-700] in uncontrolled studies have similarly concluded that trimeprazine was efficacious in the treatment of pruritus of different etiologies. (Although it is always hazardous to draw conclusions from clinical observations, the reviewers have also been impressed with the anti-pruritic effects of trimeprazine, particularly in the itching noted with chickenpox and measles. The results in patients with atopic dermatitis have not been as striking.)

The numerous untoward reactions reported from the use of the tranquilizers should caution one against their indiscriminate administration. Hollister[701] believed that allergic reactions are responsible for the most important complications from treatment with the tranquilizing drugs and described the types occurring with each group of these agents. Sensitivity to chlorpromazine may be manifested by agranulocytosis, jaundice, dermatitis and other minor reactions. Although agranulocytosis from chlorpromazine is probably of immunologic origin, conclusive proof of this mechanism still remains to be demonstrated. Reserpine is of low allergenicity but it has been noted to produce occasional angioneurotic edema, urticaria and purpura. Meprobamate sensitivity is manifested by fever, skin rashes and constitutional signs, including vascular collapse. The latter sensitivity is peculiar in that it commonly is produced by the initial dose of the drug.

The greatest number of adverse reactions have appeared to occur following the use of phenothiazine and its derivatives. Jaundice presumably on a hypersensitivity basis has been reported by Waitzkin;[702] Hollister;[703] and also Deller, Brodziak and Phillips.[704] Agranulocytosis has been reported with practically all of the phenothiazine drugs and at times has led to the demise of the patient.[705-710]

The most recent and bizarre types of reactions reported from the use of the phenothiazine tranquilizers have been their effects on the extrapyramidal tract. These reactions have occurred with almost all of the phenothiazine derivatives and are apparently quite common as evidenced by the numerous reports which have recently appeared in the literature.[711-720] Shaw and his co-workers[721] noted that in addition to the extrapyramidal effects from these agents, severe seizures may occasionally be observed. These authors emphasized that these drugs should not be used indiscriminately for symptomatic treatment without due appreciation of these alarming and potentially serious side effects which may follow relatively small doses, especially in childhood. In a letter to the editor, Goldsmith[722] suggested that caffeine sodium benzoate offers a highly effective and rapidly acting antidote when administered intravenously for these reactions. (The authors have observed in children several of these extrapyramidal effects from the administration of prochlorperazine. However, these effects have never been noted with promethazine hydrochloride (Phenergan®) although this drug has been used liberally both as an antihistamine and tranquilizer. It appears that this particular phenothiazine seems to be an infrequent cause of these unusual extrapyramidal side effects.)

Kaplan[723] reported marked hypotension in seven patients following administration of promazine (Sparine®). The reaction preceded death in three cases. The author emphasized the need for caution in the administration of such agents to patients with evidence of impending vascular collapse or severe hepatic dysfunction.

Goodman and Cahn[724] reported an adult patient engaged in handling the phenothiazine derivative, piperidylchloride phenothiazine hydrochloride, who developed dermatitis after three weeks of daily contact with this chemical.

Meprobamate, although at first considered to be relatively innocuous compared to the phenothiazine and rauwolfia derivatives, has also been shown to have some serious side effects. One of the more serious complications has been that of habituation with typical withdrawal symptoms including insomnia, vomiting, tremors, muscle twitching, anxiety, anorexia, ataxia, and less frequently, hallucinations.[725-727] The risk of addiction was found to be especially serious in patients with a history of alcohol or other addictions.[728]

Idiosyncrasies and severe allergic reactions have also been reported from this drug. Charkes[729] noted twenty-three attempted suicides and 113 anaphylactoid reactions with one death in 6,500 patients treated with meprobamate. He stated that there is no way of knowing in advance which patient will react adversely (one to 200 doses) except that allergic subjects are ten times as likely as normal individuals to do so. He advised against rechallenging with the drug in patients who have experienced anaphylactoid reactions.

ANTIHISTAMINIC DRUGS

Two comprehensive reviews of the antihistamine compounds, one by Burn[730] and the other by Michelson and Lowell,[731] have been published. These authors reviewed the physiologic and pharmacologic actions, metabolism, clinical usefulness and side reactions of these drugs.

The relative merits of Polaramine,®[732] Theruhistin,®[733,734] Diafen,®[735] Histryl Spansule®[736] and Tridecamine®[737] have been discussed by various investigators. Lawler and Limperis[738] studied a mixture of prophenpyridamine, pyrilamine and phenylephrine compounded with gallotannic acid in 100 children and concluded that the preparation was beneficial in 85 per cent of the patients. Dimetane[738-741] has also been reported to be an effective antihistamine by several authors.

McGovern *et al*[742] in a study to determine the effectiveness, dosage and toxicity of this drug administered Dimetane® to 485 infants and children. Two hundred of the patients with perennial allergic rhinitis were selected for careful follow-up studies. Good results were observed in 149 subjects, fair results in forty and poor results in eleven. Only seven patients demonstrated the side effect of drowsiness. Of interest was the inclusion in the report of two cases of marked overingestion of this drug. In neither instance were any symptoms suggesting central nervous system stimulation or other toxic symptoms noted. The authors concluded that this drug is a safe, effective antihistamine agent with a very low incidence of undesirable side effects in infants and children.

Although thenalidine tartrate (Sandostene®) has been removed from the market because of reports of hematologic toxicity,[743] several articles have appeared in the literature extolling its virtues.[744-748] (In an unpublished double-blind study using Sandostene and Sandostene plus calcium in thirty children with atopic dermatitis the reviewers found no difference in antipruritic effects between the placebo material and the drugs tested.)

Originally Gaillard[749] reported that antihistaminic therapy for gingival hyperplasia due to diphenylhyantoin was beneficial. Subsequently, a number of other investigators have found the antihistamines to be of no prophylactic or therapeutic value in its prevention or treatment.[750-752]

Gotlieb and Münz[753] reported two cases of accidental poisoning with benadryl. Both patients recovered with symptomatic treatment. The authors suggested the use of intravenous infusions of 25 per cent glucose solutions for the therapy of benadryl intoxication.

VACCINES

Both the pediatrician and allergist are vitally concerned with the untoward reactions that may occur with the administration of vaccines used in immunization procedures. Zucker and Florio[754] presented a review of the vaccines and sera available for the prophylaxis and therapy of diseases for which these agents are indicated. They emphasized that all efforts should be made to anticipate and prevent the occurrence of allergic reactions. Among measures recommended were the taking of careful, detailed histories to detect past sensitivities; skin testing with appropriately diluted antigens; in a potentially sensitive individual who must of necessity receive a vaccine or sera, they advised starting an intravenous infusion of 5 per cent glucose before administering the material; and the prior or concomitant administration of steroids or antihistamines was suggested. (There is a considerable body of evidence to indicate that the prior or concomitant administration of the steroids or antihistamines is probably of doubtful value. Certainly, it is clear that the administration of these drugs, either before or simultaneously with a potentially dangerous substance, does not insure against a severe hypersensitivity reaction. The anaphylactic reactions that have occurred following the administration of ACTH should be convincing in this regard.) They furthermore warned that a full dose of serum should never be administered to a patient suspected of being allergic to the specific material. Instead, small multiple-dose, rapid desensitization was suggested (even this procedure is not an assurance that reactions will not occur). Finally, the authors emphasized that physicians must be ready at all times to institute therapeutic procedures promptly should a reaction occur. Most of the information presented on the specific sera and vaccines available commercially was summarized in table form.

Since many species of viruses and rickettsiae require culturing in the developing of chick embryo, incorporation of inseparable egg proteins may occur during the vaccine production. The danger of administering such vaccines to egg-sensitive individuals is well known. Cohen and Mines,[755] utilizing a gel diffusion technique, studied a number of commercial viral and rickettsial vaccines to determine egg white and egg yolk components. Their results indicated a wide variation in number and types of egg components and suggested that this might be one of the determinants of allergic reactivity of a particular vaccine.

The practical importance of such investigations as Cohen and Mines' is well illustrated by the case reports of Wright.[756] This author described a near-fatal anaphylaxis reaction from typhus vaccine in an egg-sensitive individual and also reviewed the literature on the reactions observed from this specific type of vaccine.

The contamination of certain biological immunizing agents with silk from filtering through this material has been shown by several investigators to be a cause of severe constitutional reactions when the contaminated vaccine is administered to patients sensitive to silk.[757-760] (This discovery was an extremely practical and important observation. As a result of this finding the major pharmaceutical companies have changed their method of manufacturing vaccines and no longer employ silk filters.)

With the widespread mass vaccination of children and adults against

poliomyelitis, it is not surprising that a number of different types of reactions have been reported following its use. Stroud *et al*[761] described twelve patients who developed various types of dermatoses—urticarial, eczematous and psoriasiform, after the injection of Salk poliomyelitis vaccine. None of the reactions were serious, and the authors concluded that the incidence of cutaneous eruptions was extremely low. A case of erythema multiforme occurring after the first injection of poliomyelitis vaccine was described by Chervinsky.[762] Kaufman and Janeway[763] recorded a case of severe urticaria, angioedema, fever, leukocytosis, arthralgia, myositis, lymphadenopathy and radiculitis in a twenty-year-old nurse starting nine hours after her third Salk vaccine injection. Extensive immunologic studies failed to prove which antigenic component in the vaccine was the etiological excitant.

Although many of the reactions observed from polimyelitis vaccine are severe, it is apparent that the incidence of these reactions is very low. Christensen[764] in analyzing 184 million doses of vaccine noted there were only 146 significant reactions. Of these, thirty-seven were neurological in nature and fifty-six were allergic. Baumann and Felder[765] analyzed the incidence and nature of the reactions which occurred after a total of 138,528 first and second doses of poliomyelitis vaccine. Local reactions at the injection site occurred in about 15 per cent of the group. Fever developed in twenty-nine patients within twenty-four hours after the injection. Urticaria and other types of rashes were observed in twenty-four patients; asthma occurred in three cases; polyarthritic symptoms were noted in two. Various forms of neurological complications were noted in seven patients. All of the reactions were usually of brief duration, subsiding within a few hours or days after the vaccination.

It has also become quite evident that many of the serious reactions that have been observed following poliomyelitis vaccination are due to minute quantities of penicillin or streptomycin that are present in some vaccines.[766-772] (Poliomyelitis vaccines are now available commercially which do not contain penicillin. These preparations should be used for immunizing against poliomyelitis in any individuals who are known or suspected of being sensitive to penicillin and in severely allergic patients who are highly sensitive to a number of antigens.)

Several authors have reported severe untoward reactions following the administration of influenza vaccine.[773-776] Denny[773] described the development of generalized urticaria in a five-month-old child given 0.1 ml of influenza vaccine intracutaneously in the volar surface of the forearm. A severe vascular (anaphylactoid) purpura occurring a few days after the administration of a polyvalent influenza vaccine (A and Asian strains) was also reported by Stefanini *et al.*[774] Immunologic studies in their patient revealed antibodies against the specific vaccine but not against its allantoic fluid constituent. A subcutaneous reactivation test was positive, and a passive transfer (Prausnitz-Kustner) was successful. No sensitivity to egg protein or the preservative used could be demonstrated by *in vivo* tests. The authors postulated that the symptoms presented by the patient could be due to a serum sickness type of reaction to one of the constituents of the vaccine, probably due to the virus protein itself and that the local reaction observed simulated an Arthus phenomenon. An unusual local allergic reaction of previously vaccinated skin occurring in response to a systemic Asian flu infection was described by Zelman.[775] Griffin[776] reviewed the procedures and materials used in the vaccine manufacture of influenza vaccine, as well as the incidence and type of reactions noted in military personnel.

The author concluded that influenza vaccine led to less "time lost from reactions than other common immunizing agents."

Several studies have appeared comparing the effectiveness of intradermal vaccination to subcutaneous immunization for influenza vaccine. Sanger[777] from his studies concluded that the rise in antibody titer produced by the administration of 0.1 ml of influenza vaccine intradermally was comparable to that achieved with subcutaneous injection of 1.0 ml of the same vaccine. A consultant answering a question in regard to the efficacy of various routes of immunization was also of the opinion that the intracutaneous method of administration of vaccine was a satisfactory method for immunization.[778] McCarroll and Kilbourne[779] concluded that equivalent small doses by the subcutaneous or intradermal routes were at least equivalent in antigenic efficacy. Their findings indicated that a division of the vaccine into two separate injections given seven days apart produced a response superior to that effected by the same total dose in a single injection. (The intradermal route of administering vaccines offers the additional advantage of diminishing the number of constitutional reactions.)

Although a vaccinia infection superimposed on eczematous skin lesions (previously discussed in the section on atopic dermatitis) is the most frequent complication of smallpox vaccination encountered by the allergist, other serious reactions have been observed. Boehm[780] presented a general discussion of these complications and described an eleven-month-old infant with a prolonged, progressive vaccinia eventually necessitating amputation of the arm and shoulder girdle. In this unusual case, hyperimmune vaccinia gamma globulin administered repeatedly did not check the progression of the lesions, and there was no evidence of hypogammaglobulinemia. Galloway and MacBean[781] and Cramblett *et al*[782] similarly described a patient who developed vaccinia lesions without any underlying skin disease from contact with a patient with a primary take. Of practical importance in this paper was the description of a rapid method for detecting the presence of vaccinia virus utilizing tissue culture and serologic techniques. An apparently rare complication of smallpox vaccination was reported by Kisch.[788] He described a patient who developed Guillain-Barre syndrome following a severe primary take. He postulated that this syndrome was a hypersensitivity reaction to the smallpox vaccination and reviewed the evidence supporting this thesis. Acute pericarditis after a smallpox vaccination was described by Cangémi.[784]

Kibrich and Kunz[785] reported two cases of vaccinia of the lip. One of these occurred at the site of a healing herpetic lesion and was a consequence of smallpox vaccination during attempted prophylaxis of recurrent herpes simplex. (In view of this occurrence of vaccinial infection superimposed on the herpes simplex lesion and because of the questionable evidence as to the value of repeated smallpox vaccinations for the prevention of recurrent herpetic infections, the reviewers are in agreement with these authors that a further assessment should be made of this procedure.)

Muth[786] reviewed some of the common and uncommon reactions that have been noted following vaccination with BCG. He reported a case of regional suppurative adenitis with associated caseous tubercle formation following the percutaneous type of vaccination in a three-day-old infant. The author speculated that the lymphadenopathy resulting from the vaccination with BCG is a distinct clinical entity.

It is obvious that a vaccine which could materially reduce the incidence of respiratory infections in allergic children would be of invaluable aid to those charged with their management. Recently, vaccines to some of the

newly recognized respiratory viruses have become commercially available. Using one of these vaccines, a polyvalent adenovirus type, Chobot *et al*[787] injected sixty-three allergic children with this preparation. Pre- and post-vaccination titers were obtained, and the authors noted unexpectedly high pre-injection titers in many of the allergic children. They also noted higher titers via the intradermal route than those produced via the subcutaneous route. No conclusions were drawn in regard to the efficacy of this preparation in preventing respiratory infections. (These authors' findings of high titers prior to immunization correlate well with those of Jordan, Badger and Dingle.[788] These latter authors demonstrated that children five years of age had adenovirus antibodies of types 1, 2 and 6 which were comparable to those titers observed in adults. Since the adenovirus group probably are not responsible for more than 1 per cent to 5 per cent of the respiratory infections in children, it is doubtful that the administration of this particular vaccine will have any beneficial use in the treatment of allergic children. Furthermore, vaccine mixtures of respiratory viruses of all those presently identified might still be ineffective since the etiology of more than 70 to 80 per cent of respiratory infections remains unknown.[789,790])

Tetanus and problems relating to its prevention and treatment still constitute a major challenge to the medical profession. Edsall[791] in a review article prepared for the AMA Council on Drugs presented one of the most complete and lucid dissertations on the prophylaxis of tetanus that the reviewers have read. Since this article does not lend itself to abstraction, we recommend that it be read in its original form.

There still appears to be some disagreement and confusion with regard to the simultaneous use of tetanus serum and toxoid in the prophylaxis of tetanus. Recent studies by Eckmann,[792] Bergentz and Phillipson,[793] and Prudovsky and Turner[794] indicate that active immunization with tetanus toxoid administered simultaneously in a different site with tetanus antitoxin serum is a very useful procedure which does not materially affect the antitoxin response to the toxoid.

Hampton and Hard[795] have suggested the possible use of aluminum phosphate-adsorbed tetanus toxoid being administered intradermally in 0.15 to 0.2 ml doses in order to produce an active immunity within seven to ten days. When this technique is used, occasional superficial ulcers and nodules at the site of injection were noted in a few of the subjects. (This type of immunization should not be used in lieu of passive immunization whenever a tetanus-prone wound is being treated.)

Wall[796] discussed in general the use and abuse of tetanus antitoxin in acute injuries. The author believed 40,000 to 100,000 units of tetanus antitoxin are necessary to insure adequate protection against tetanus-prone injuries.

In the immediate treatment of tetanus, Turner, Velasco-Joven and Prudovsky[797] suggested the intravenous administration of tetanus antitoxin in a single dose of 40,000 to 80,000 units. If sensitivity to horse serum occurs (as manifested by the intradermal test) he suggested 1 ml of epinephrine chloride 1:1,000 to be given intramuscularly fifteen minutes before the administration of antitoxin and an antihistamine drug to be added during the first few hours of treatment. He reported that sixty-two patients manifesting intradermal sensitivity were thus treated without occurrences of symptoms suggesting anaphylactoid shock. (In spite of the relatively large numbers of patients treated by this technique, the prophylactic measures recommended by these authors will not prevent the onset of anaphylaxis in all patients. In a patient who had a clinical

history of being sensitive to horse serum or manifests a positive scratch, intradermal or eye test to diluted horse serum, it would be best to administer bovine tetanus antitoxin. If this is not feasible, then small doses of the tetanus antitoxin horse serum should be first administered intradermally. If no untoward reactions occur, subsequent doses may be increased and administered subcutaneously, intramuscularly and finally, if necessary, intravenously. In the prophylactic treatment of tetanus in patients who are sensitive to horse serum, it is preferable to use a tetanus immune globulin which has been prepared by the Cutter Laboratories of Berkeley, California. Unfortunately, because of the limited supply of this product, it is only being distributed in California at the present time. This gamma globulin should not be confused with that ordinarily used for the prophylaxis of measles, hepatitis or poliomyelitis.)

INSECT ALLERGY

Allergic reactions to insects have been the subject of a number of papers recently published in the literature. Based on their studies, Wiseman and his co-workers[798] suggested that common antigens are present in the various life cycles of the same insect as well as in different members of the same order. They also demonstrated a considerable number of skin-test reactions to insects in allergic patients and postulated that these reactions may be of clinical significance in allergic respiratory disease, especially the seasonal type. Perlman[799] presented an excellent general review article on insect allergy which included a discussion on the experimental evidence that insects can produce allergic reactions, the aerobiology, biochemistry, and preparation of insect antigens, and, in addition, reported his clinical observations. Of 252 unselected patients tested with extracts of various arthropods, crustacea and arachnids, positive skin-test reactions were observed in 50 per cent of the patients. There appeared to be no striking correlation between the reactions to insect allergens and the more common allergens used in testing patients. Eighty-three of his patients were under specific hyposensitization with allergic extracts, but Perlman believed these patients have not been observed long enough to be able to draw any definite conclusions as to the beneficial effects of this therapy.

The remaining papers on insect allergy were all concerned with some aspect of hypersensitivity reactions to bees, wasps, hornets and yellow jackets. Case reports and general reviews of this subject were recorded by several different authors.[800-802] Parrish,[803] after analyzing death certificates of all patients who died from the bites and stings of venomous animals and insects in the United States from 1950 through 1954, concluded that such casualties are much more common than generally realized. He found 215 deaths listed during this period and observed that some deaths from insect allergy were probably certified as "heart attacks" or "heat strokes."

In the treatment of generalized reactions to bee and wasp stings, Seijffers[804] concluded that intravenous noradrenaline seemed to be superior to the injection of epinephrine. (The reviewers believe epinephrine to be the drug of choice for immediate anaphylactic reactions from any cause. Noradrenaline should be administered intravenously as a supplement in those individuals who remain in shock.)

Morse and Ghent[805] listed a number of protective measures that should be taken against stinging insects. These authors suggested light-colored clothing made of smooth fabric, as well as the avoidance of leather and suede clothing, scarves over the head, and perfumes and other types of scented cosmetics. Slow movements in the presence of bees was also advised

except if a swarm of insects is encountered. Following a sting by a honey bee, the stinger and venom sac should be removed as quickly as possible by scraping the skin. They also pointed out that bees are rarely found when the temperature is below 60° F, and therefore less likely to be encountered on a cool day.

Ordman[806] described his procedure for the prophylactic desensitization of persons sensitive to bee sting with increasing strengths of whole-bee extracts administered intracutaneously and reported successful desensitization in nineteen persons who were highly sensitive to bee stings.

Mueller[807,808] has published two papers on his experiences with severe allergic reactions to insect stings. Based on studies of eighty-four patients with severe systemic allergic reactions, Mueller noted that multiple sensitivities usually occur. Furthermore, those with a family history of allergy had the more severe reactions. He recommended serial intracutaneous skin testing using a polyvalent extract of bee, wasp, hornet and yellow jacket and that treatment should always be started at the 1:100,000,000 dilution level. Mueller noted that: (1) The more severe the sting reaction, the greater the skin sensitivity; (2) The identification of the insect causing the sting reaction is unreliable unless the insect is brought in by the patient; and (3) Patients tested ten days after reaction had little skin sensitivity and the question was raised whether these patients were in a refractory state. Finally, he reported the results of seventy-six patients treated with hyposensitization techniques; 40 per cent of these individuals have had subsequent stings and only one subject had any systemic symptoms.

In an effort to solve some of the problems of cross reactions and cross-sensitivities to the stings of the Hymenoptera insects, Foubert and Stier[809] studied antigens made of wasps, yellow jackets, yellow hornet, black hornet and honey bee by anaphylactic studies in guinea pigs and gel diffusion techniques. The two methods were confirmatory. Each insect demonstrated one or two antigens common to the others and at least three or four specific antigens. Antigens varied in their ability to sensitize and to shock. Yellow jackets seemed to be the most potent sensitizer while black hornet was the least. Bee antigen evidenced the least degree of cross reactions both by gel diffusion and anaphylaxis. These authors concluded that desensitization to these insects should be carried out using a combined antigen of yellow jacket, hornet, wasp and bee, particularly where the offending insect cannot be accurately identified and where there is any possibility of a multiple sensitivity.

SERUM PROTEINS IN ALLERGIC DISEASE

The relationship of the serum proteins, especially gamma globulin, to immunity and the diseases of hypersensitivity has been investigated by a number of workers. Gittlin, Gross and Janeway[810] have written a very exhaustive, excellent review on some of the biochemical characteristics of gamma globulin, the clinical conditions associated with disturbances in gamma globulin metabolism, and the clinical situations in which this substance may be used for prophylaxis and therapy. Of particular interest to the allergist was the discussion of blocking, skin sensitizing and other types of antibodies in relation to gamma globulin; the occurrence of delayed hypersensitivity reactions and an arthritic condition resembling rheumatoid arthritis in agammaglobulinemia patients and the use of gamma globulin in the treatment of generalized vaccinia.

Because of the serum-protein changes in asthmatic individuals previously noted by other investigators, Stroh and Ericksen[811] reinvestigated the prob-

lem to determine whether the changes were specific for the allergic state. A comparison of serum electrophoretic patterns of chronic asthmatic patients, subjects with other allergic conditions or histories of infection and normal individuals was made. The subjects consisted of forty-two adults and twenty-three children. From their data the authors concluded that it appears that there is no specific change which can be detected by routine electrophoretic studies in the serum-protein patterns of asthmatic children or adults. The changes noted by the methods employed in their investigation did not appear to be characteristic for any of the particular pathological conditions studied. In a similar study of twenty-three typical atopic dermatitis patients and twenty-three well-matched controls by Pickrel and Derbes,[812] no differences could be determined in serum paper electrophoretic patterns.

Tuft[813] reported finding serum protein abnormalities in a group of 121 children suffering from intractable asthma. The cephalin cholesterol flocculation was abnormal in 49 per cent of the patients. Increased thymol turbidity and zinc turbidity and positive zinc flocculation tests occurred with much less frequency. Although abnormal reactions to one or more of the tests were general, the number of increased reactions to the individual tests varied considerably and bore no relationship to each other. The administration of prednisolone tended to lower temporarily the incidence of abnormal cephalin flocculation tests. There appeared to be no correlation between the abnormal liver function tests and the general increase in gamma globulin levels which the author stated occurs in asthmatic patients.

Since Bowen's[814] original favorable report on the use of gamma globulin in the treatment of asthmatic children and the subsequent report by Bernton,[815] there has been considerable interest in the possible use of gamma globulin for the treatment of this condition. A well-designed double-blind control study, conducted by Abernathy, Strem and Good,[816] among twenty-two severely allergic children indicated that treatment with gamma globulin appeared to have no beneficial effect on the course of chronic asthma. Fifteen of the total sample improved clinically; eight were in the treatment group and seven were controls. No significant differences were noted in the amount of asthma, physical growth, hemoglobin value, or eosinophilia between the two groups. Frequency of infectious disease was approximately the same in treatment and control groups as among the normal children of the same age range (one and a half to fifteen and a half years).

Further studies on the use of gamma globulin in the treatment of intrinsic asthma were done by five different physicians in a cooperative study under the auspices of the drug committee of the Academy of Allergy.[817] Eighty-four children, all under twelve years of age, who had asthma associated with infection, were given gamma globulin 0.5 cc per kilogram body weight and the dose repeated every two weeks for three injections. Determinations of gamma globulin by electrophoresis or chemical methods were done prior to and at the end of the gamma globulin therapy. A total of six infants under one year were studied. Low gamma globulin levels were found in this age group (which is a normal finding particularly in infants under three months of age and which has recently been ascribed by Trevorrow[818] as being primarily due to dilution in an expanding plasma volume). In three of the four patients who showed improvement, there was also a rise in gamma globulin levels. (Taking serial blood levels of gamma globulin irrespective of the administration of gamma globulin would also probably show an increase in these levels.) The authors concluded that in the older age group, "gamma globulin does not appear to affect the course of infectious asthma

materially, although some clinical improvement did occur in most cases." (Use of a double-blind controlled technique as in Abernathy's *et al* study would have been helpful in clarifying the usefulness of gamma globulin in the treatment of infectious asthma.)

Heyn and Carroll[819] studied the problem of whether or not the "physiological" drop in the level of gamma globulin during the first six months of life has any relationship to the antibody response in the infant. Serum gamma globulin levels were done on a series of mothers and their infants in correlation with a poliomyelitis vaccination study. Their preliminary studies suggested to the authors that there is not a close correlation between the globulin levels and the antibody responses obtained.

Mathesiu and Maly-Plzen[820] carried out passive immunization of 150 premature infants with intramuscular gamma globulin 0.3 cc per kilogram in an attempt to prevent staphylococcic infection in the premature infant, and felt that the incidence of infection was significantly lowered and that eventually its manifestations were postponed.

Two cases of acquired hypogammaglobulinemia were reported by Painter and Korst.[821] One of these patients had infectious asthma associated with an eosinophilia. This latter patient was able to form alpha-2 and beta globulin, fractions which have been purported to contain the allergic antibodies or atopic reagins. Aziza and Lapin[822] also reported the case of a three and a half-year-old boy who experienced repeated episodes of pneumonia associated with eosinophilia, as well as one episode of severe status asthmaticus and who had an associated hypogammaglobulinemia. The patient was treated with the administration of 10 cc of gamma globulin every two weeks plus the use of erythromycin and ACTH or cortisone. The authors also reviewed the literature on Loeffler's syndrome and gamma globulin deficiencies.

Oberman *et al*[823] studied levels of gamma globulin in various infections and hypersensitivity states. Paper electrophoretic analysis was performed on the sera of 239 children of varying ages suffering from selected bacterial, viral and hypersensitivity diseases, and in seventy-eight children subject to repeated infections. Abnormally high levels of serum gamma globulin were most frequently found in children with rheumatic fever, glomerulonephritis, infectious hepatitis, tuberculosis and bacterial infections in which lymphoid tissue was locally involved in the pathologic process. Bacterial meningitis, bronchial pneumonia, aseptic meningitis and common viral infections usually did not raise the level above the normal range. In the majority of the cases, when abnormal values occurred, they were observed during the first week of illness and the level was usually again within the normal range or falling toward it by the fourth week of illness. Abnormally low levels of serum gamma globulin were primarily found in children with lipoid nephrosis and in infants under seven months of age. It was not possible to correlate diagnostic or prognostic criteria for any illness with any alterations in the serum gamma globulin levels. Children with low gamma globulin levels could not be clinically differentiated from those subject to repeated infections who had normal or high serum levels of gamma globulin.

A dysgammaglobulinemic syndrome was described by Hammack, Bolding and Frommeyer.[824] These authors reported globulin peaks in electrophoretic patterns from the serum of four patients with unusual susceptibility to infection. Although immunologically the serum proteins of three of the patients were related to multiple myeloma proteins, this diagnosis could not be established. The fourth patient's serum proteins were related to macroglobulin. The term of dysgammaglobulinemia was coined to imply that these

four patients had a disturbed function of the gamma globulins which is manifested by repeated infections and also that there may be multiple etiologies for this disturbance.

Baybutt[825] reported a possible hypersensitivity reaction to immune serum globulin. The term of dysgammablobulinemia was coined to imply that these immune serum globulin (human) intramuscularly and sixty seconds later developed symptoms resembling anaphylactic shock. The infant was treated with epinephrine, prednisolone and seconal rectally, diphenylhydramine and later with oxygen and oral prednisolone. The child had no history of any previous allergic reactions. Studies of the gamma globulin preparation in question revealed it to be sterile and free of pyrogen. Excerpts of a letter by Dr. Charles A. Janeway are quoted in the report. Janeway speculated that the reaction observed was allergic in nature but could not rule out a vasomotor reaction which occurs with intravenous injection of gamma globulin. In his discussion on the mechanism of the reaction he postulated that "atopic reagins" from the mother may have been present in the infant and reacted with food antigens present in the administration of gamma globulin. (This possibility seems unlikely since maternal reagins are not by present techniques demonstrable in newborn infants or, in other words they do not appear to cross the placental barrier. The reviewers believe that Janeway's second suggestion of a vasomotor reaction is the more likely explanation for the difficulties encountered in the child.)

SKIN AND OTHER ALLERGIC DIAGNOSTIC TESTS

Zall and Heimlich[826] in a study of young adult medical students, found that a history of clinical allergy, personal or familial, would usually forecast positive skin test reactions. On the other hand, if the student were unable to recall any allergic symptomatology or knew of no familial history of allergy, negative skin tests were likely. In their study of sixty-one medical students, twenty-eight who were atopic and thirty-three nonatopic, the authors were able to predict the skin test reactions in 71 per cent of the atopic group and in 69 per cent of the nonatopic group. From their studies and experiences, the authors concluded that the ability of an instructor in pediatric allergy to demonstrate the relative predictability of skin testing in medical students is a useful teaching technique.

The general use of skin tests and their abuse was discussed by Unger[827] and by Horesh.[828]

The Committee on Food Allergy of the Academy of Allergy investigated the various methods by which allergenic food extracts are prepared as a basis for other studies which would enable the allergist to prepare more uniform and active allergenic food extracts.[829] A questionnaire was sent to all members of the Academy, and the results published in the *Journal of Allergy*. The methods used contained many variables, and it was obvious that further investigation of the entire problem of standardization of allergic extracts is necessary. Perlman,[830] in an excellent article dealing with the quality and reliability of allergens in skin testing, outlined some of the techniques which he considered to be important in the preparation of good allergenic extracts and described the method of acetone precipitation which he feels is the best technique available. To support this latter contention, he presented his comparative studies of various commercial extracts and his acetone-precipitated materials. An editorial in the *J.A.M.A.* highlighted the fundamental problems of standardization of extracts and emphasized that further investigations in this area are necessary.[831]

Cohen and his co-workers,[832,833] using the gel diffusion technique, have

demonstrated a wide qualitative variation among individual component antigens of both fish and crustaceans in homologous species skin-testing extracts of different laboratory sources.

Tuft *et al*[834] evaluated the clinical usefulness of eye tests in relation to skin tests for the same allergens and to the patient's history of sensitiveness. The results of this evaluation indicated to these authors that the eye test was especially helpful in the following situations. (1) To determine the presence or absence of clinical sensitivity in patients with positive skin tests but negative or doubtful clinical history. (2) As a means of uncovering unsuspected etiologic factors in patients with negative skin tests and an indefinite clinical history. (3) To affirm the nonclinical nature of positive skin tests in the patients with negative clinical histories.

Using the original method of Prausnitz and Kustner, Ratner[835] evaluated the passive transfer test in sixty-eight different "receptor" children between eight and fourteen yars of age. The author found that the antibody responsible for the positive test was not present in the blood of allergic individuals at all times. Neither were antibodies to all allergens to which an individual was sensitive necessarily present at any one time. In addition, some persons were incapable of acting as successful receptors. Therefore, he felt the test is "unreliable and should be regarded as inadequate as a diagnostic procedure, despite its convenience." (Nevertheless, passive transfer tests may be useful under certain clinical experimental conditions.)

Degara[836] reported a case of homologous serum hepatitis which was presumably due to passive transfer skin test studies done on the father of an eight-month-old infant with atopic eczema. (The reviewers also know of a recent case of homologous serum hepatitis which presumably developed secondary to passive transfer skin tests being performed for experimental studies. Although the risk of this type of complication would be minimal in carrying out passive transfer skin testing restricted to one series of tests, it is obviously magnified with repeated testing and with multiple donors in the same recipient subjects.)

Ratner, Crawford, Feldman and Krimli[837] studied 103 children to determine whether the delayed allergic reactions which frequently follow serum injections might be an intermediate stage of hypersensitivity and not necessarily one that is unique or distinct from the immediate type of reaction. From their data, these authors concluded that their studies lent support to the possibility that in some instances the delayed tuberculin-type reaction may represent an intermediate stage of hypersensitivity.

London and Glaser,[28] in a study of 400 allergic patients who were skin tested with egg white, presented some interesting findings as well as their own speculations as to the significance of this test. The subjects were divided into four different groups as determined by age: Group I—none to two years; Group II—three to six years; Group III—seven to twenty-one years and Group IV—over twenty-one years—and were classified as to their allergic diagnoses. Egg white skin tests were performed by both the scratch and intradermal techniques, the latter being omitted with a strongly positive scratch reaction. The reactions observed were then correlated with the clinical sensitivity. Several unexpected findings were observed by the authors. First, in the youngest age groups the skin test was positive in less than half the patients (42 per cent) in the presence of clinical sensitivity. Secondly, the number of infants clinically sensitive to egg white, but giving negative skin tests, increased as age advanced. Thirdly, more than one-third (34 per cent) of the group reacted positively to egg white but were not clinically sensitive. Of the entire group, only about one-half of all patients

who reacted to egg white were clinically sensitive. In their discussion, the authors presented a tenable theory as to why positive cutaneous test to egg white (or other foods) may be clinically significant in atopic dermatitis, even though the test does not reproduce the type of dermatitis being studied. (Since the authors postulate that some of the positive skin tests observed in early infancy might have been the result of a primary histamine or serotonin-releasing substance present in the egg white, it would have been interesting to know how many of the positive reactions observed in the non-clinically sensitive group were from intradermal skin testing and also what the incidence of positive reactions using the same antigens would have been in a group of normal individuals. Information of this type would perhaps throw some light as to the histamine or serotonin-releasing effects or other non-specific irritating effects of the particular egg white antigens used and also be informative as to why an incidence of 70 per cent positive reactions to egg white was observed in this series in contrast to only 20 per cent of the comparable series reported by Ratner and Untracht.[838])

In 1956 Black[839] published "a new diagnostic method in allergic disease" which involved the motility and viability of human leukocytes when dried, powdered allergens were mixed with the patient's serum. In an effort to confirm Black's studies, Chambers, Hudson and Glaser[840] were unable to obtain similar results. These authors found the test difficult to perform, time-consuming and difficult to interpret. (In a verbal report of a similar attempt to utilize this test, Heimlich[841] likewise was unable to confirm Black's results. Thus, it is clear that this "new diagnostic method" for determining clinical sensitivities as described by Black is technically difficult and the results of the tests open to some question.)

Errigo *et al*[842] studied the skin reactivity of normal subjects and of allergic subjects to pollens and histamine during prednisone treatment. The prednisone did not appear to suppress the skin test response; but, on the other hand, in 50 per cent of the cases, tuberculin reactivity in patch tests was inhibited or attenuated when the patient was receiving prednisone. (This observation, which has been previously demonstrated, enables one to prepare the severely wheezing patients and those subjects with generalized atopic dermatitis for adequate direct skin testing.)

Sills, Rom and Berk[843] found that repeated skin testing with histoplasmin may give rise to a false positive reaction due to an apparent induced skin sensitivity. This type of reaction was not observed with repeated skin testing with old tuberculin or coccidioidin.

EOSINOPHILIA

Although the significance of eosinophilia remains obscure, the presence of these cells in the respiratory tract secretions has long been considered as presumptive evidence of respiratory allergy. Thus, it is of considerable practical interest that Matheson *et al*[95] have demonstrated in normal infants within the first few months of life a nasal, blood and stool eosinophilia which could not be correlated with any family history or manifestations of allergy. (Although the mechanism of the origin of eosinophilia in infancy is not known, it is clear that the finding of eosinophilia in this age group cannot be interpreted as evidence of an allergic reaction.)

Arnoldsson and Helander,[844] in studying the problem of eosinophilia in allergic individuals, reported that 50 per cent of all of the allergic subjects studied showed a blood eosinophilia. They studied the diurnal rhythm of eosinophil cells in the peripheral blood of sixteen normal and twenty-two

asthmatic subjects. As has been demonstrated by others, the eosinophil count in normal subjects declined during the morning hours and thereafter rose gradually until it reached a maximum between midnight and 3 a.m. In their asthmatic patients, this diurnal rhythm was reversed, the eosinophil count being maximal between 9 a.m. and 11 a.m. and minimal between midnight and 3 a.m. Hedström[845] similarly found that the blood eosinophil count in asthmatic patients usually lacks the normal tendency to fall in the morning hours and to rise in the afternoon. (A possible explanation of this reversal of the eosinophil pattern would be that these subjects are producing an increased amount of corticosteroids in the evening in response to the stress of their asthma which in turn suppresses the eosinophil count.)

A number of rare diseases in infants and children have been shown to be associated with marked eosinophilia. One of these conditions is the recently recognized clinical syndrome of visceral larva migrans. It is characterized by persistent marked eosinophilia, leukocytosis, hyperglobulinemia and hepatomegaly and is usually found in infants or children who had close contact with household pets or were in the habit of eating dirt. Usually the diagnosis of the syndrome can be made with considerable certainty on clinical grounds alone, and the prognosis for the syndrome is favorable. Wong and Laxdal[846] reported an additional case of this syndrome in an eighteen-month-old infant.

Another rare condition which must be added to the entities which are associated with eosinophilia in infants and children is lymphopneumatosis cystoides intestinalis (intestinal emphysema). Gagnon and Rheault[847] reported five cases of this condition associated with an eosinophilia in infants. They pointed out that the exact pathogenesis of this condition remains obscure, as well as the origin of the eosinophilia.

An increasing number of cases of idiopathic hypoprotinemia have been reported in children. In addition to being characterized by depletion of serum albumin and most of the serum globulin fractions and an occasional iron deficiency anemia, many of these patients have also had an associated eosinophilia. This latter finding has suggested to some investigators the possibility of a hypersensitivity mechanism as the etiology of this syndrome.[848,849] The etiology of "idiopathic hypoproteinemia" has recently been demonstrated, at least in some cases, to be due to a loss of plasma proteins into the gastrointestinal tract without an associated actual bleeding.[850-853] (How this "abnormal bowel function" arises, however, has still not been clarified, and although eosinophilia has been an associated finding in some of the cases, to the best of the reviewers' knowledge, no hypersensitivity mechanism has been shown to be involved in this pathological process.)

POLYARTERITIS AND ALLERGIC ANGIITIS

Although polyarteritis and allergic angiitis are considered by some to be identical diseases, there is considerable confusion in the definition of these syndromes, and some investigators have attempted to differentiate them as separate entities. In answer to an inquiry sent to the editors of the *J.A.M.A.* a consultant pointed out some of the differentiating features of these syndromes.[854] Clinically, both conditions are characterized by fever, malaise and protean symptoms due to involvement of multiple organ-systems. Typically, the onset of allergic angiitis can be precisely related to the administration of a drug or exposure to certain chemicals, and there is usually a history of hypersensitivity to other agents as well. Eosinophilia, bronchial asthma and cutaneous manifestations such as purpura and subcutaneous nodules are seen more commonly in allergic angiitis than in polyarteritis

nodosa. In addition, some pathologists claim that these conditions can be distinguished histologically as well as clinically, even though the basic lesion in both is an acute arteritis of all the small arteries with necrosis and polymorphonuclear infiltration of the vessel wall. The author also pointed out that, from a practical point of view, it is not too important to be able to differentiate these diseases. The differentiation is usually only of academic interest for the treatment and prognosis are not too dissimilar.

Rose[855] as well as McCarthy and Kesten[856] reviewed the clinical and pathological features of polyarteritis and other forms of allergic vasculitis. McCombs[857] also discussed allergic vasculitis as a common primary lesion in a number of clinical pulmonary disorders which included Loeffler's syndrome, rheumatic fever, rheumatoid arthritis, periarteritis nodosa, "allergic" vasculitis, allergic granulomatosis, systemic lupus erythematosus, sarcoidosis, beryllium pneumonitis, hexamethonium pneumonitis and the Hammon-Rich syndrome. It was his belief that the early recognition of the allergic vasculitis is important since the course, which is usually a progressive development of pulmonary fibrosis, can be checked by the administration of the corticosteroid drugs. Komrower, Macgregor and Marsden[858] described a child of nine years of age with a superior vena caval thrombosis associated with periarteritis nodosa.

Although necrotizing arteritis is being reported more frequently, it still remains a relatively rare disease in infancy and only eighteen cases have been reported with onset during the first year of life. Munro-Faure[859] added another case and reviewed the literature of this syndrome. Some of the cases showed predominant and often isolated involvement of the coronary and myocardial vessels. These cases also exhibited fairly characteristic manifestations—fleeting macular skin eruptions, fever, leukocytosis with or without eosinophilia, conjunctivitis, pharyngitis, cervical adenitis and cough. Seven of the cases, which did not have coronary involvement, presented in a variable way. The etiologic theories, including the hypersensitivity hypothesis, were discussed and the author recomemnded early institution of steroid treatment as a possible method of management of infants presenting a similar diagnostic problem.

MISCELLANEOUS

Several general articles on the management of allergy in childhood have appeared.[860-862] McGovern[861] presented some of the basic principles on which the therapy of allergy rests. These were divided into two main theses: (1) the concept of allergy as a process of "reaction to injury" (disease processes as reaction patterns called forth from the body in response to trauma or injury) and (2) the "threshold" concept (resistance level at which injury is sufficient to precipitate allergic disease). Both of these concepts are clearly illustrated diagrammatically and other conditioning factors—such as infection, meteorological factors, emotional aspects, constitutional predisposition—which may also modify the allergic reaction shown. In discussing therapy specifically, avoidance of allergens is stressed by the author, but other measures—symptomatic, supportive, prophylactic therapy—are also briefly discussed.

In an excellent synoptic paper Logan[862] presented in a clear diagrammatic fashion the current knowledge of the mechanism of acute allergic reaction. In this illustration the author showed the concepts of antigen penetration, antibody production, the relation between antigen and antibody, the substances released by antigen-antibody reaction, as well as the role played by the various therapeutic measures in the treatment of acute allergic reac-

tions. (Logan's method of presenting the subject was to digest an extremely complex and controversial topic, and present a tremendous mass of facts in a simple manner. However, as he points out, the diagram should not be viewed as a complete and final explanation of the immediate allergic reaction, but merely summarizes some of our present knowledge and, as well, highlights some of the areas of the allergic reaction that are still poorly understood. In the reviewers' opinions, this paper should be read by all pediatricians interested in the subject of allergy.)

Ordman[863] reviewed the manifestations of childhood allergy—respiratory, dermal and gastrointestinal—in more than 900 allergic children from birth to twenty years of age. As has been reported elsewhere, the incidence of respiratory allergy in boys was two to three times that found in girls in the birth to five years of age group, but thereafter the incidence was approximately the same. More than 80 per cent of the patients developed their seasonal hayfever before twelve years of age and more than 50 per cent had already developed symptoms of vasomotor rhinitis by the fifth year. The author also discussed the control of childhood allergy with special reference to elimination of allergic foodstuffs, the avoidance of inhalant allergens or specific hyposensitization against them, and the importance of psychological influences.

McLeod[864] and Stafford[865] presented general discussions of methods of prophylaxis for allergic disease in children. Both authors stressed the avoidance of highly allergenic foods in early infancy, as well as the early and continued treatment of any allergies that do develop.

Crook, Harrison and Crawford[866] in a concise, well-organized and timely paper, presented their views on some of the controversies that have surrounded allergy and allergists over the past few decades. They pointed out that there has been a relative neglect of allergy in the fields of medical research, education and practice. In the field of practice they cited their own experience that 14 per cent of all the patients coming to their general pediatric clinic had major unquestioned allergic disease.[867] In spite of allergic problems being easily the second most common problem encountered in private practice, the first being infections of various types, the authors admitted their feelings of inadequacy in facing this situation and presented other evidence that their feelings are not unique among pediatricians. They further speculated as to some of the possible causes for resistance, skepticism and dislike for allergy that are often present in the minds of many physicians and patients. One of the factors, they felt, is that physicians dislike things about which they know very little. The second factor considered was that the techniques used in allergy are complicated, time-consuming, and results of treatment are often not dramatic. Other reasons presented for these negative attitudes toward allergy were: (1) the nature of the disorder and the gaps in our fundamental knowledge are such that it is difficult for scientifically trained and academically-oriented medical personnel to "pin down" allergy in a precise manner; (2) allergy has received very little from the public in the way of financial support for research; (3) finally, the dislike for allergy is accentuated by the marked disagreements and differences of opinion among leaders in the field. "It is small wonder that cynical skeptics listening to the confusion of the voices of the allergic babel incorrectly consider the whole of allergy to be so much hocus-pocus or quackery."

In spite of the discouraging picture painted, the authors felt that there were some hopeful trends—development of sub-specialty qualification in pediatric allergy and better training facilities resulting in better trained al-

lergists and pediatricians. As a solution to the complex problem, the authors offered these suggestions: (1) devote more time to teaching of allergy in the curriculum of medical schools and intern and residency programs and integrate this teaching into the general practice training program; (2) the adoption of more open-minded attitudes by non-allergist pediatricians and educators; and (3) finally, further basic research in allergy, immunology, chemistry, and other related fields would seem essential. (The reviewers would add to these suggestions the development of more full-time academicians interested in teaching and doing research in the field of allergy so that they in turn could develop a more complete training program for pediatricians interested in the sub-specialty of pediatric allergy.)

Criep[868] presented his results of management of 972 allergic patients who were under treatment for at least a year's period of time. Among Criep's patients, those under the age of twenty years were found to have much better prospects of marked relief from bronchial asthma, perennial nasal allergy and atopic dermatitis than did older people. This effect of age was not seen in the case of hayfever, but patients with hayfever were much more likely to obtain relief than were patients in the other three categories. Gregoire and Comeau[869] also reported on the results of treating 1,000 cases of asthma and rhinitis. Of the asthmatics and patients with allergic rhinitis, approximately 10 per cent remained unimproved.

Physical findings supposedly characteristic of allergic children have been described by Cohen[870] and by Nassau and Kelner.[871] Cohen claimed that a tuft of hair over the vertex of the skull, which is difficult to make stay down with a comb or brush, is a premonitory sign of allergy. Nassau and Kelner's sign of allergy was a wrinkling of the skin in the region of the elbow. (The reviewers have not been impressed with the frequent occurrence of these signs in allergic children. Furthermore, these signs occur so commonly in normal children that it is doubtful that they are indicative of allergic disease.)

A general discussion of constitutional allergic reactions and their prevention is presented by Waldbott.[872] Preventative measures and prompt initiation of therapy when these reactions occur is stressed by the author.

Glaser, Aponte and Barsky[873] in a two to twenty-seven-year follow-up study of 614 newborn or very young infants in whom the diagnosis of thymic hyperplasia had been made by roentgenogram and treated with x-ray irradiation found that 173 (28.2 per cent) were afflicted with asthma, hayfever or eczema as compared to 8.2 per cent of 1,287 siblings who were not irradiated. From this study the authors concluded that the presence of an unusually broad mediastinal shadow presumably due to the presence of an enlarged thymus gland or the presence of respiratory symptoms, which could be conceivably attributed to the presence of an enlarged thymus gland, are reasonable presumptive evidence that such a child is more likely to develop subsequent allergic disease than the child who does not present such findings. (Because enlarged thymic shadows are seen so frequently in normal infants and because such marked variations in the size of the gland can be observed with changes in respirations, the gland appearing larger during the expiratory phase, caution should be exercised in attributing large mediastinal shadows as evidence of potential allergic disease.)

Collins-Williams[874] clearly enumerated some of the many differences in the manifestations, course, diagnosis and treatment of allergy in the younger age groups as compared to adults. He pointed out that in the younger age groups (1) food allergies play a greater role, (2) the allergic manifestations are more apt to change, (3) the prognosis is better, (4) different diseases

must be considered in the differential diagnosis, (5) fewer drug reactions occur, (6) acute respiratory infections more frequently precipitate attacks, and (7) there is greater opportunity for prophylactic measures. Collins-Williams rightfully emphasized that the differences between allergy in children and adults are of degree rather than absolute. Nevertheless, for the proper care of the allergic patient it is essential for the allergist to recognize these differences.

As part of a symposium on iatrogenic disease, Deamer[875] covered several areas of difficulty produced by the physician. Among those topics discussed were constitutional reactions resulting from testing and hyposensitization. Mention was also made of flaring atopic dermatitis patients when ordinary doses of antigen are given. For this reason Deamer did not feel that hyposensitization for atopic deramtitis is indicated. An additional danger to the child with atopic dermatitis is exposure to vaccinia virus by either direct vaccination or immunization of a contact. Other problem areas alluded to were the "tension state" produced when parents are told their child is allergic, the untoward effects from the administration of drugs; the difficulties resulting from dietary changes; and the problem of tonsillectomies and adenoidectomies in allergic children. Finally, he mentioned the potential danger of administering horse serum to an allergic individual.

During the past few years another of the so-called "non-specific cure-alls" for allergic diseases has been reported.[876-879] This product, an extract of *Toxicodendron quercifolia,* is marketed under the trade name of Anergex (Rx) and is advertised as "the injectible which inhibits the allergic response" and, consequently, suppresses allergic manifestations regardless of the offending allergen. This drug was studied by the Committee on Drugs of the Research Council of the American Academy of Allergy and was found in sixty-nine patients treated by four different investigators to have no striking therapeutic effects.[880] The committee considered any further study as being unwarranted. A controlled study, using the double-blind placebo method, was utilized by Kamin *et al*[881] to evaluate the effects of the administration of this drug in the treatment of allergic children. Thirty subjects received the extract and twenty-six received comparable injections of normal saline. Six weeks after the onset of treatment the children were re-evaluated. No statistically significant differences between the groups could be ascertained. However, it was quite remarkable that approximately 66 per cent of the children in each group were improved, thus demonstrating that the positive attitude on the part of the doctor treating an allergic child has considerable importance. (It is indeed unfortunate that year after year new drugs and agents, without proper evaluation, are brought forth and heralded as being a cure-all for allergic diseases. By merely being exposed to a widespread advertising campaign, many naïve and uncritical physicians, in their search for more suitable therapeutics to treat these chronic diseases, are deceived by the promise of wonderful results. By virtue of their placebo effects, as was beautifully demonstrated by Kamin *et al* in the previously mentioned study, the use of these products is often perpetuated.)

Existing data indicate that there is a marked impairment of the newborn infant's ability to form various types of antibodies. Smith, James, Eitzman and Miller,[882] however, found that prematures and newborns have the capacity to respond to the H antigen of the organism *E. typhosa.* On the other hand detectable anti-O antibodies were present in only one serum of the sixty-two infants studied. Ultracentrifuge studies showed that the actively produced antibody to the H antigen was of the 19S type, and its

role in the natural defense mechanisms is being further investigated by these authors.

Another phase of immunity at birth was studied by Edwards, Griffiths and Swift.[883] The phagocytic activity of the leukocytes of cord blood and the leukocytes of the mother were measured in unheated cord, maternal and normal adult serum and in heated cord, maternal and adult serum. These authors concluded from their data that the cord serum is relatively deficient in a heat-stable factor capable of enhancing phagocytosis and that the leukocytes of cord blood are less dependent upon the heat-labile factors in serum than are maternal leukocytes. The heat-stable fraction of maternal serum most effectively enhances phagocytosis by cord leukocytes.

Two general papers on immunology have appeared in the pediatric literature.[884,885] In one of these papers Raffel categorized the immunologic diseases on the basis of their underlying immunologic mechanisms. Raffel[884] classified immunologic mechanisms producing disease into two general groups: hypersensitivity and cytotoxicity. Diseases of hypersensitivity depend in general upon the reaction between an antibody and a foreign antigenic substance. Such reactions account for anaphylactic shock, atopic hypersensitivities, serum sickness and polyarteritis nodosa. There is some question as to whether rheumatic fever, disseminated lupus erythematosus, rheumatoid arthritis, glomerulonephritis and demyelinating encephalomyelitis should not also be included. In the other main group, that of cytotoxicity, the mechanism is thought to be a direct action of antibodies upon the cells or tissues and Raffel subdivides this group into three kinds of mechanisms. In the first subgroup the author includes those diseases in which iso-immunologic reactions are involved; for example, erythroblastosis, tissue and organ grafting, etc. The second group encompasses those diseases whose origin was due to the development of autoantibodies, the situation where an individual becomes sensitive to his own tissues. Finally, in the third subcategory under cytotoxic effects, diseases in which antibodies are directed not against the cell itself but rather against an extraneous substance (such as a drug or virus) adherent to it. Certain drug-induced anemias, purpuras and leukopenias depend on such a mechanism. In the final portion of his paper Raffel discussed the nature of the evidence necessary for establishing a human disease as one of immunologic origin. The evidence comes from two sources: (1) clinical observation and experimentation and (2) experiments on lower animals. He pointed out some of the deficiencies in our knowledge of these diseases and some of the pitfalls of relating certain diseases etiologically to immunologic mechanisms.

In the second article Najjar and Robinson[885] reviewed their concepts of the mechanism of antibody-antigen reaction and related this concept to clinical, allergic, and immunologic disease states. The theory that these authors proposed is based on the premise that when an antibody molecule reacts with an antigen molecule there is produced in the resulting complex a simultaneous alteration of the surface configuration of the two components. By these changes this new complex in turn becomes antigenic in nature and specific antibodies form against the new antigenic sites of the complex. This process of new complexes with respective antibodies being formed continues until the original antigen disappears from the body of the subject, or when no further alteration in the surface configuration is obtained.

Based on studies of fifty-two cases of meningococcemia infection, Margaretten and McAdams[886] suggested that the vascular thrombosis appeared to be the primary lesion involved in the production of the hemorrhagic lesion

of the skin and adrenals and suggested that these lesions may be produced by a local Schwartzman phenomenon. Of special interest was the occurrence of three instances of renal cortical necrosis, such as is seen characteristically in the generalized Schwartzman reaction. Because of the similarity of the lesions found in the fatal cases of meningococcus infection with the Schwartzman phenomenon and the fact that cortisone is one of the most efficient methods of potentiating the Schwartzman phenomenon, the author questioned the wisdom of the use of the adrenal steroid therapy in fulminating meningococcus septicemia. It was also found that of 156 patients with meningococcus infection not in shock at the time of admission there was a mortality of 21 per cent for the patients who received adrenal steroid therapy compared with the 7 per cent mortality in those who did not receive adrenal steroids. (Another possible explanation for the increased mortality noted in the steroid group is that these agents were selectively administered to the more critically ill patients.)

Lange, Wasserman and Slobody[887] reported that following serum complement levels has been helpful in the diagnosis and prognosis of acute and subacute glomerulonephritis. In acute cases of glomerulonephritis there is a marked lowering of complement levels. With clinical healing there is a return of complement to normal levels almost simultaneously. However, persistence of the disease in the subacute stage is usually associated with continued low complement levels.

Heiner[888] described a test for the diagnosis of histoplasmosis using precipitin reactions in agar gel. He felt the test appeared to have a greater sensitivity and specificity than currently available tests for histoplasmosis and found it was useful in clarifying some of the problems of cross reactions and false positive reactions than have been noted with some of the older methods.

Recently interest has been focused on the leukocyte antibodies which, although known to exist for some time, are now thought to be of considerable clinical importance. Excellent comprehensive editorial reviews on this subject have been recently published both in this country and in Britain.[889,890] Two cases of congenital transient neutropenia in newborn infants of neutropenic mothers were described by Stefani.[891] The authors believed that these children were examples of a hitherto unrecognized syndrome, probably due to the transplacental passage of the neutropenic factor. Neutropenia in each case persisted for about four weeks when normal values for the leukocytes in the blood became established. The pathogenetic classification of neutropenia and a discussion of the relevant literature were also provided.

Page and Good[892] reviewed the literature on the rare disease, cyclic neutropenia, and presented a case of their own intensively studied over an 11-year period. The basis of the cyclic neutropenia appeared to be cyclic failure of neutrophilic maturation. Although extensively sought for, no evidence of the appearance of a factor injurious or destructive to neutrophils was found in the peripheral blood at any time.

Tullis[893] described a simple test for the detection of antileukocyte antibodies. The effects of mixing the normal leukocytes and heterologous leukocyte serums were observed for decreased motility of the neutrophils, agglutination and in the more potent antiserums, hyperbrownian movement and lysis. Antileukocyte activity was demonstrated in serums from a wide variety of hematologic diseases with leukopenia.

Brittingham and Chaplin[894] presented immunological evidence to suggest that febrile transfusion reactions can be caused by sensitivity to donor leukocytes and platelets.

Rorsman[895] studied the relationship of histamine to the number of baso-

phil leukocytes in the blood in a number of allergic conditions. The author found that the number of basophil leukocytes is significantly decreased in some cases of urticaria but not in asthma or atopic dermatitis.

It seems likely from experimental evidence in animals and the demonstration of antibodies to the thyroid gland or thyroglobulin in humans that thyroiditis and possibly other thyroid conditions in man can be classified as autoimmune diseases. Blizzard *et al*[896,897] by hemagglutination and gel diffusion techniques studied a number of thyroid diseases for evidence of antibodies to human thyroglobulin. These antibodies were found in thirty-four of ninety-four patients with thyrotoxicosis, in seven of ten with spontaneous myxedema, in eight of nineteen with nontoxic nodular goiter, in three of five with chronic thyroiditis, in one of eighteen with athyrotic cretinism. The postulated mechanism for the production of these antibodies is that an insult to the thyroid gland liberates thyroglobulin from the thyriod follicle. Thyroglobulin, which is not normally present in the circulation, gives rise to specific antibodies. The subsequent reaction of the antibody to the antigen then produces lymphocytic replacement or destruction of the thyroid cells or both. Blizzard has also presented some evidence suggesting that in certain cases of athyrotic cretinism the placental transfer of maternal antibodies to thyroglobulin might produce destruction of the fetal thyroid. In confirmation of Blizzard's *et al* studies, Cline, Selenkow and Brooke[898] have also demonstrated antibodies in some of their patients with miscellaneous thyroid disorders including acute and subacute thyroiditis. The autosensitization concept of the etiology of thyroiditis is further discussed by Beare.[899] In addition, thirty-three cases of this disease are presented and based on this material, the clinical features, diagnosis, pathology and treatment were described.

In an evaluation of atmospheric mold spores as allergens in the New York metropolitan area, Merksamer and Sherman[900] found mold sensitivity most frequently in the younger age groups, 78 per cent occurring in the first decade of life and 17 per cent in the second decade. These authors concluded that mold sensitivities are an important cause of respiratory allergy in the New York metropolitan area from about the middle of June to about mid-November.

Rooks and Shapiro[901] discussed the value and limitations of mold surveys by the culture plate method. They felt that the application with electrostatic precipitation to impingement in the sampling instrument increased the sampling efficiency for both *Alternaria* and *Hormodendron* spores. A new method for the preparation of mold extracts using a synthetic medium was also described by Schaffer, Molomut and Center.[902] The authors concluded that the new media eliminated most of the non-specific, allergenic and other interfering factors which are commonly found in other used media. Criep Teufel and Miller[903] reported on the use of fungicidal agents in the treatment of allergy to molds. Of the agents investigated, Roccal (Zephiran) and trioxymethylene were found to be satisfactory and thought to be helpful in the therapy of several mold sensitive patients.

BOOKS

An excellent book which covers the entire field of pediatric allergy has been written by Sherman and Kessler.[904] The book, entitled **Allergy in Pediatric Practice,** has several outstanding features—presentation of some of the basic scientific background for diagnostic and therapeutic procedures used, practical suggestions for the management of the major allergic problems occurring in children, a good index for ready reference, and a style of

presentation of the subject matter which makes the book easy to read. This book is recommended for all those who are interested in pediatric allergy.

Speer[905] has also published a book on the management of childhood asthma. It is a concise, practical book consisting of 116 pages which, however, is directed more to the level of the student and physician who is not familiar with the fundamentals of allergy.

An entire volume of the Pediatric Clinics of North America was devoted to pediatric allergy.[906] Authoritative discussions by different authors of almost every phase of pediatric allergy were included in this symposium. Although a few of these discussions have been referred to in the body of this review, most of these excellent papers, because of their review nature, were purposely omitted. This volume should be of interest to both the pediatrician and allergist.

SUMMARY

The authors have attempted to review the literature on pediatric allergy, a subject which encompasses all of allergy. For that reason, many articles pertaining indirectly to pediatric allergy have been included in this review. Undoubtedly many other worthy papers have been inadvertently omitted from the review; to these authors we apologize. We would also like to emphasize that any criticisms made in the review merely reflect the opinions and experiences of the reviewers, and as Disraeli once said, "It is much easier to be critical than to be correct."

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5830 Overhill Dr.

The Shape of Things to Come

Methods for preparing isotonic solutions by means of graphs or tables on the basis of experimentally found iso-osmotic values.
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A study of the anaphylactic mast-cell reaction *in vivo* following desensitization of sensitized guinea pigs.
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Papers of Interest

Barre, E., Danrigal, A., Richier, L. L., and Le Branchu, F.: A histamine globulin complex. Initial clinical results in therapy of asthma. Presse med., 68:29 (Jan. 9), 1960.
Of fifty patients, twenty-two reported excellent results. There were fourteen others who improved and another fourteen in whom there was no change.

Ishida, Nakao, Kosaka, Yasumi, and Sasaki, Yuichiro: Studies on experimental influenza in mice. II. Absolute amount of virus introduced into the respiratory tract of mice by standard inhalation procedure. Tohoku J. Exp. Med., 71:151 (Dec.) 1959.
The extent to which it is possible to dilute virus suspensions, and still kill 50 per cent of the mice tested, is compared, using in some cases the technique of inhalation, and in others the technique of instillation. One tenth to one sixteenth of the virus was effective at the time of inhalation, as compared with the values obtained at the time of instillation.
P^{32}-labeled virus was prepared, and the actual count found along the whole respiratory tract, as well as in the lung, was compared between the two groups of mice infected by these two procedures. Only one-tenth as much virus was found in those rats infected by the inhalation procedure.

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The distribution of the virus in the mice's organs, both thirty minutes and three hours after injection from three different routes, was examined by means of radioactivity.
From the results obtained in this study, the concept of the pneumotropism of influenza is discussed.

Mozan, A. A.: Chymotrypsin therapy of peptic ulcer. Postgrad. Med., 26:542 (Oct.) 1959.
Following 4,666 intromuscular injections of aqueous chymotrypsin in seventy-eight patients with peptic ulcer, two mild systemic and one anaphylactic responses were noted.

Robinson, William D.: The use of adrenocortical steroids in diseases of connective tissue. University of Michigan Med. Bull., 25:355 (Oct.) 1959.
A balanced review.

Kahn, Milton M., and Levy, Edwin J.: A comparison of topical corticosteroids: triamcinolone acetonide, prednisolone, fluorometholone and hydrocortisone. AM&CT, 6:734 (Dec.) 1959.
More rapid and complete involution of dermatological lesions was obtained with triamcinolone acetonide than with prednisolone, fluorometholone, or hydrocortisone in 222 patients in a double-blind, paired comparison study.

Finnerty, Edmund F., Jr.: Triamcinolone in dermatologic conditions. New England J. Med., 262:176 (Jan. 28) 1960.
Review of treatment of eighty-eight patients.

Logue, John T., and Barrett, James T.: Repeated nonfatal anaphylactic shock from intramuscular penicillin. AM&CT, 6:672 (Nov.) 1959.
A case of repeated nonfatal anaphylactic shock reactions due to penicillin injection in an otherwise nonallergic patient is recorded. Painful local reaction occurred due to penicillinase injection. Circulating antibody could not be demonstrated by immunological techniques, using the patient's serum and penicillin-coated donor cells, or by passive cutaneous anaphylaxis tests in the guinea pig.

Sciple, George W., Know, John M., and Montgomery, C. Hunter: Incidence of penicillin reactions after an antihistaminic simultaneously administered parenterally. New England J. Med., 261:1123 (Nov. 26), 1959.
In a controlled study of a series of 4,367 patients, an antihistaminic was ad-

ministered simultaneously with penicillin to determine if the incidence of penicillin reactions could thereby be reduced. Benzathine penicillin, procaine penicillin with two per cent aluminum monostearate in oil and chlorprophenpyradine maleate injected intramuscularly were the agents used.
Chlorprophenpyradine maleate in 10-mg and 20-mg doses injected muscularly with penicillin did not decrease the incidence of voluntarily reported penicillin reactions as compared to the control group.

Makari, Jack G.: Some recent studies in the immunology of cancer. I. Detection of methyl-cholanthrene-like substance by the Schultz-Dale method in the sera of patients with tumors and in some apparently healthy persons. J. Geriatrics Soc., 7:611 (Aug.), 1959.
With the use of the sediment obtained from aqueous carcinoma centrifuged at 3,200 to 4,000 rpm, results which were highly specific for carcinoma (96.8 per cent positive in carcinoma and only 4.8 per cent positive in noncancerous lesions) are reported. Burrows confirmed these findings in a large series of cases. He obtained 96.7 per cent positive results in carcinoma, and only 3.3 per cent positive results in noncancerous lesions. This procedure could well serve as a specific diagnostic test for carcinoma.

Makari, Jack G.: Recent studies in the immunology of cancer. II. Demonstration of antibodies to cancer polysaccharides and to polysaccharide-antibody complexes by an intradermal reaction. J. Geriatrics Soc., 8:4 (Jan.) 1960.
Evidence for the immunologic activity of melanoma-sensitizing substances and polysaccharide-like substance when injected intradermally into man.

Makari, Jack G.: Recent studies in the immunology of cancer. III. Detection of cancer antibodies and auto-antibodies by intradermal reactions, with a review of the detection in human serum of cancer antigens by the Schultz-Dale method. J. Geriatrics Soc., 8:16 (Jan.) 1960.

Fox, Everett C.: The treatment of common skin diseases. G. P., (July) 1959.
Complete version excellent. Summary in Current Med. Digest, 26:116 (Nov.), 1959 equally good.

Banyai, Andrew L.: Cough and its management in elderly patients. Geriatrics, 14:621 (Oct.), 1959.
Expert in field advances. Reasoned triple approach to vexatious problem.

Koprowski, Hilary: Viruses 1959. Trans. N. Y. Acad. Sci., 22:176 (Jan.) 1960.
A learned, well-written, enjoyable historical review.

Lozano, F. Fernadez: The pathogenic bacterial flora of the respiratory tract in different types of asthma. (In Spanish.) Revista Clinico Espanola, 74:359 (Sept.) 1959.
Ventilatory efficiency (capacity to take up oxygen per unit of ventilated air) is studied in a series of patients with respiratory disease subjected to different operations. Ventilatory efficiency is in inverse relation to basal ventilation and when it fails, owing to the fact that its potential is exhausted, hyperventilation occurs. Ventilatory efficiency is greater in the diseased or collapsed side, and also greater in middle- or upper-lobe lesions than in those at the base. The mechanisms of ventilatory adaptation fail in lung resection.

Innerfield, I.: Physiological and clinical effects of buccally given proteases, J.A.M.A., 170:925 (June 20), 1959.
Trypsin, streptodornase, and streptokinase are effective by the buccal or the parenteral route.

Prasad, Ananda S.: Severe urticaria following erythromycin therapy. New England J. Med., 262:139 (Jan. 21) 1960.
A case of urticaria so severe that erythromycin therapy was discontinued.

Boger, William P., and Gavin, John H.: An evaluation of tetracyline preparations. New England J. Med., 261:827 (Oct. 22) 1959.
Fifteen tetracycline preparations were studied. The magnitude of observed differences between tetracycline preparations are largely of academic interest. The best preparation appears to be unembellished tetracycline chloride.

News Items

INTENSIFIED COURSE IN THE USE OF EMULSIFIED EXTRACT

Under the auspices of The American College of Allergists, an intensive two-day course concerned with the use of emulsified extracts in the treatment of respiratory tract allergy will be conducted on Saturday and Sunday, May 27-28, 1961, at the Pick-Congress Hotel, Chicago, Illinois, by a small group of physicians headed by Dr. Ethan Allan Brown of Boston. This course will deal with the technical and clinical aspects and applications of this important advance in the method of treatment. Lawrence J. Halpin, M.D., Cedar Rapids, Iowa, will act as Chairman and Moderator, with Morris A. Kaplan, M.D., of Chicago, and Clifford H. Kalb, M.D., of Milwaukee, as Co-Chairmen.

Saturday, May 27, 9 to 12 a.m. and 2 to 5 p.m., will be given over to intensified instruction and explanation of the technical preparation and demonstration of the emulsions currently employed in the practice of allergy. There will be an informal buffet supper, featuring an excellent menu, during which there will be ample opportunity for informal discussion with Doctor Brown and other allergists now employing this type of treatment, and with two of Doctor Brown's technicians who will be in attendance.

Instructions and demonstrations will be resumed on Sunday morning, May 28, from 9:00 through 12:00 o'clock. Sunday afternoon, from 2:00 to 4:00, will be devoted to the instruction of technicians. Physicians registered for the course may also attend the Sunday afternoon session.

A registration fee for the course of $25.00 will be charged, and all physicians are urgently advised to make their registrations in advance. Attendance will be restricted to bona fide allergists and will be open to all Fellows and members of the two national allergy societies, The College and the Academy, and to all members of regional, state and city allergy societies. Each allergist enrolled and in actual attendance will be permitted, without the payment of any additional fee, to co-register one technician in his employ. Only one technician for any physician may be co-registered, and no technician may be registered alone.

Address all communications regarding reservations and any inquiries regarding arrangements to: Eloi Bauers, Executive Vice President, The American College of Allergists, 2160 Rand Tower, Minneapolis 2, Minnesota. Telephone: FEderal 2-2948.

PRELIMINARY REPORTS

Physicians are invited to send a preliminary report of papers which they plan to publish or present at state, regional or national meetings to the *Review of Allergy and Applied Immunology,* 75 Bay State Road, Boston, Massachusetts.

The reports should be from 250-500 words in length and pertinent to some aspect of allergy or immunology or their related fields. The appearance in the *Review* of these abstract-like reports will not preclude the publication of the full-length paper in any other journal.

BOOK REVIEWS

YEAR BOOK OF DRUG THERAPY. Edited by Harry Beckman, M.D. (1960-1961 *Year Book* Series) 587 pages. Price: $8.50. Chicago: The Year Book Publishers. 1961.

How does Beckman do it? Year after year, the Year Book of Drug Therapy maintains its high level of excellence. The 1960-1961 series begins with studies of drugs in allergy. Reviewed are Dimetane, Triaminic, and Hydrocortisone. Sandostene, Dexamethasone, Aristocort (in long term treatment), other corticosteroid hormones and cortisones, all prescribed for use by mouth and, as well, corticosteroids injected intranasally, are all reviewed.

Studies of oral theophylline compounds, choline, theophyllinate, hydro-alcoholic theophylline and the perennial problem of aminophylline toxicity, especially in children, all receive their fair share of attention. The differences between ipecac in syrup and fluid extract form are emphasized by means of a case report of stenosing esophagitis subsequent to the use of the extract.

Beckman ranges far afield but pertinently discusses Atarax, Varidase, Norisodrine, atropine cigarettes and Pamine bromide.

In all, the abstracts derive from fourteen journals, with seven from the ANNALS OF ALLERGY, three from the *British Medical Journal,* two each from the *New York Journal of Medicine* and *California Medicine.* From all of the other weekly, monthly and bi-monthly publications, only one paper each was selected for abstract and comment.

Four excellent papers in the field of broncho-pulmonary diseases are discussed, namely those concerned with chemoprophylaxis, progesterone, THAM for respiratory acidosis, and the treatment of pulmonary embolism with fibrinolysin.

Cardiac disorders, as usual, receive 103 pages of abstracts; the steroids, five; and dermatologic maladies, twenty-two. The treatment by drugs of every aspect of medicine is covered by the remaining 400-odd pages.

A poll would surely elect the Critical Evaluation of the Year's New Drugs as the most important feature of this book. Following an introduction and title, the Basis for Judgment of a New Drug, every therapeutic agent from those amebicidal to those used in the treatment of vulvovaginitis is critically reviewed.

For allergic patients, there are the one-ingredient preparations, Twiston, Tacaryl, Isopro and Duratab aminophylline. Of Anergex, Beckman says, "My feeling is that when controlled studies are made with this agent, it is not likely that more than placebo effects will be revealed."

Of the two-ingredient preparations, there are Actifed, Disophrin and Isoclor. The three-ingredient preparations include Personamine, Tridecamine Dospan, Prednamin and Polanil. There are also four-ingredient preparations as Decominic, and Napril, and one with five ingredients, Bronkotabs. It "does" everything, with ephedrine for decongestion, theophylline for bronchodilation, thenyldiamine for antihistaminic action, phenobarbital for sedation and glyceryl guaiacolate for antitussive action. It does not contain an ataractic agent, and no expectorant is included. Perhaps these will be available in next year's model.

One apt quotation characterizes Beckman's point of view:

"An important question is whether we should drop any drug whose use has been shown to be associated with considerable risk of serious toxicity or reaction of hypersensitivity. Certainly in the recent past the answer would have been a categorical 'Yes,' but at present one cannot be so dogmatic. The fate of the untreated population at risk must be taken into account, for we have today reached a point in pharmaceutic and pharmacologic advance when the possibility of ameliorating the symptoms of a vast number of pathologic states is explorable if there is the willingness to

take a certain risk. The disease, the person and the circumstances must be taken into account in each case. Withhold chloramphenicol (Chloromycetin) because numerous instances of hematopoietic damage have occurred, some of them fatal? Certainly, if other less toxic antibiotics will handle the infection as well; certainly not, if the organism involved has developed more resistance to other available antibiotics than to chloramphenicol, or if the diagnosis is typhoid fever, which only this drug will control. Withhold aminopyrine (Pyramidon), a most efficacious analgesic, because agranulocytosis has sometimes been associated with its use? Certainly, in all instances, because there are other drugs of practically equal effectiveness in the types of pain in which aminopyrine itself would be useful. The phenothiazine derivative compounds (Thorazine, Pacatal, Trilafon, Compazine, Sparine, etc.) have been associated with numerous side effects and serious toxicities, but abandonment of this group is not to be seriously contemplated until it can be replaced by less harmful agents that are just as efficacious in neuropsychiatric practice. You must simply realize that when you administer a phenothiazine derivative, a cortisone in a patient with an active or latent infection, pentolinium (Ansolysen) in an elderly patient with prostatic enlargement, etc., you are sitting on a powder keg and will find it advisable not to smoke (i.e., not to relax your therapeutic vigilance) while so doing. Just being alive even in a healthy state involves great risk in itself. I believe that the physician is justified in adding to that risk in the hope of canceling out an additional one—if he has reached his decision to do so with full knowledge of what is involved and is sure that he can cut his losses with good conscience."

The reviewer heartily concurs.

E.A.B.

THE CHEMISTRY OF IMMUNITY IN HEALTH AND DISEASE. By David W. Talmage, M.D. and John R. Cann, Ph.D. 178 pages. Price: $5.25. Springfield, Illinois: Charles C Thomas, 1961.

The present volume is directed toward an integrated biological and chemical consideration of immunology, especially the production of antibodies, their physical and chemical properties, and the mechanism, thermodynamics and kinetics of the antigen-antibody reaction. These fundamental biochemical and immunochemical questions are introduced by placing them in the more general concept of host-parasite relationships and such acquired changes as "adaptive" enzyme production in bacteria. Later, antigen-antibody specificity is similarly placed in the larger field of the relation of protein structure to biological activity. Finally, the physico-chemical aspects are supplemented with an appendix on chemical equilibrium and thermodynamics.

The interplay, not always harmonious, of ideas from clinicians, biologists and chemists has had an honorable history in immunology and has given the present discipline much of its vigor. The present cooperative effort by a biologist and a physical chemist should therefore be most welcome to all workers in the broad field of immunology.

—From the Preface by Dan H. Campbell, California Institute of Technology and W. H. Taliaferro, University of Chicago.